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ACTA PÆDIATRICA

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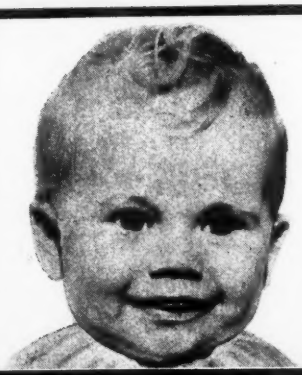

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C I B A

Acta Pædiatrica **46**: 317—320. July 1957

From the Paediatric Department, University Hospital of Lund
(Head: Prof. S. Siwe, M.D.)

The "Lente" Insulins in Juvenile Diabetes

by GUNNAR ENGLESON and ORLA LEHMANN

The introduction of the Insulin Zinc Suspensions (the Lente Insulins) in the treatment of diabetes mellitus in 1951 by Hallas-Møller *et al.* (1, 2) has been followed by a number of papers (3–13) dealing with various aspects of the clinical value of these new insulins. As to the chemical and pharmacological problems of these insulins reference is made to Hallas-Møller *et al.* (1, 2).

The present study was started in 1952 and a preliminary report concerning the first 22 patients was published by one of us (G.E.) in 1953 (3).

The material now presented consists of 42 cases in all. Most of the cases from the first report have been re-investigated in recent years. Thus the period of observation varies from 1 to 4½ years. The material consists of 23 girls and 19 boys, aged 2–17 years, with a mean age of 10.7 years.

The children were admitted to the Paediatric Department, University Hospital of Lund for stabilization on the Lente Insulins. They were all kept on a dietary regimen of constant caloric value.

Blood sugar determinations were carried out at intervals six times during the day and night for six days. Mean curves ("daily profiles") for these six days were plotted and from these curves the average blood sugar as well as the delta blood sugar (Δ B.S.) was calculated (Hallas-Møller *et al.* (1, 2)). The Δ B.S. refers to the difference between the highest and the lowest value of the blood sugar curve. Glucosuria was simultaneously estimated.

During these tests as well as later on, after their discharge from hospital, all the children were put on a regulated dietary regimen. Throughout the test period each of the patients was kept on a constant insulin dosage.

Blood sugar curves from diabetics treated with a constant diet and insulin, have been found to have three typical shapes, named A, B and C-reactions (Hallas-Møller *et al.* (1, 2)). The A-reaction (◡) is characterized by a rapid decrease in blood sugar during day-time and an increase during the night and the C-reaction (◠) by higher blood sugar values during the day and lower during the night. The B-reaction is characterized by fairly equal values throughout day and night (—).

This method opens up new possibilities of estimating the adjustment of the diabetic state. A low Δ B.S. has often been found to be correlated with the B-reaction type of the blood sugar curve. A good chemical control of

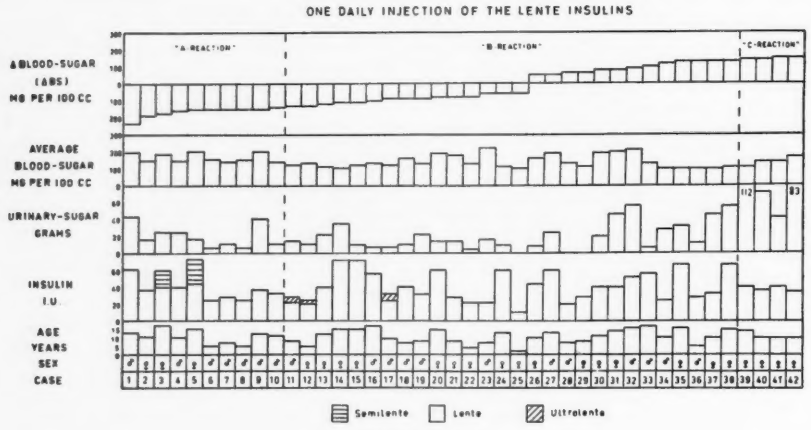

Diagram.

the diabetic condition is obtained by a Δ B.S. of 125 mg/100 ml in adults, and a Δ B.S. of 150 mg/100 ml in children, who are likely to have more unstable blood sugar reactions.

The result of the present investigations is illustrated in the Diagram. Of the 42 patients 5 were new diabetics. The remaining 37 patients had been treated earlier with different insulins, and some of them had had 2 daily injections.

In 28 children, i.e. in about 70 per cent, a Δ B.S. below 130 mg/100 ml was obtained, and as many as 37 patients (88 per cent) had a Δ B.S. below 150 mg/100 ml.

Thus a B-reaction type of the blood sugar curve could be obtained in about 70 per cent; there were 10 children with an A-reaction and 4 patients with a C-reaction.

The average blood sugar was in the majority of cases below 200 mg/100 ml and the mean urinary excretion of glucose was 22 g (2 extremely high values excluded).

All children could be controlled by a single dose of insulin, but after their discharge from hospital three patients had to have 2 daily injections in order to establish a good adjustment. These three children were 15–17 years old and their insulin requirements were high, i.e. between 60–80 IU a day.

The mean insulin dosage was 40 IU. The adjustment of some girls at puberty was difficult, but afterwards satisfactory adjustment could be re-established.

Most patients felt better after establishment on the Lente Insulins. It

should also be emphazised that insulin reactions were rare, although the blood sugar values were often rather low.

That the Lente Insulins are superior to other commercial insulins in the treatment of diabetes is shown by the rapid growth of some of the children 1–2 years after their establishment on the Lente Insulins. There are reasons to believe that this rapid growth is due to a normalization of the carbohydrate metabolism, caused by the Lente Insulin, but it should also be noted that insulin by itself has growth-promoting properties (Salter and Best, (14)). In order to elucidate this increase in growth the data in 5 cases are given below.

Case 1 G. S. ♂ 13 years.—History of diabetes for seven years. From 9–10.5 years of age the patient grew 1.5 cm (¾ in.) and from 10.5–12 years of age on Lente 12 cm (5 in.).

Case 2. L. N. ♂ 15 years.—Diabetes for nine years. From 10.5–12 years of age the increase in height was 2.5 cm (1 in.). During the following one and a half years on Lente the increase was 7.5 cm (3 in.).

Case 3. B. N. ♂ 11 years.—Diabetes for five years. From 7–8 years of age the boy grew 4 cm (about 1.5 in.). After change to Lente the increase in height during the first year was 7.5 cm (3 in.) and during the following one and a half years 8.5 cm (about 3½ in.).

Case 4. A–L. ♀ 12½ years.—Diabetes for nine years. From 8–10 years of age the girl grew 8 cm (about 3¼ in.). During the following 2 years on Lente the increment was 17.5 cm (7 in.).

Case 5. M. N. ♀ 13 years.—Diabetes for six years. From 9–11 years of age the increase in height was 7.5 cm (3 in.) and from 11–13 years of age on Lente 11.5 cm (4½ in.).

Summary

The following is an account of investigations carried out at the Paediatric Department, University Hospital of Lund on the treatment of juvenile diabetes with the Lente Insulins.

The material comprises 42 patients, aged 2–17 years. In 37 cases (i.e. 88 per cent) a Δ blood sugar below 150 mg/100 ml was obtained. During establishment on the Lente Insulins we noted in some cases a substantial increase in height. Insulin reactions were rare and most patients felt better after changing to Lente Insulin.

L'insuline « lente » dans le traitement du diabète juvénile.

Résultats obtenus avec l'insuline « lente » dans le traitement de cas de diabète juvénile. Quarante-deux patients âgés de 2 à 17 ans ont été traités. Dans 37 cas (soit 88 %), le taux de la glycémie put être ramené en dessous de 150 mg/100 cm³. Une augmentation notable de la croissance en hauteur a été observée dans certains cas durant le traitement par l'insuline « lente ». Les réactions d'intolérance à l'insuline furent rares et la plupart des malades se sentirent mieux après le passage à l'insuline « lente ».

„Lente"-Insulinpräparate bei jugendlichem Diabetes.

Bericht über die Behandlung von jugendlichem Diabetes mellitus mit „Lente" Insulinpräparaten. 42 Kranke im Alter von 2–17 Jahren wurden auf diese Weise

behandelt. In 37 Fällen, d.i. bei 88 %, wurde ein Blutzuckerspiegel von unter 150 mg/100 ml erreicht. Während der Behandlung mit „Lente" Insulin kam es bei manchen Fällen zu einer wesentlichen Zunahme im Körperwuchs. Insulinreaktionen waren selten und die Mehrzahl der Patienten wies eine Besserung im Allgemeinbefinden auf, wenn sie auf „Lente" Insulinpräparate umgestellt wurden.

Insulinas «Lente» en la diabetes infantil.

Se expone el tratamiento de la diabetes mellitus infantil con insulinas «Lente». Fueron tratados cuarenta y dos pacientes de 2 a 17 años de edad. En 37 casos (es decir el 88 %) se obtuvo un delta de azúcar en la sangre inferior a 150 mg por 100 ml. Durante el tratamiento practicado con insulinas «Lente», se observó un aumento apreciable de la estatura en algunos casos. Se produjeron rara vez reacciones insulínicas y la mayoría de los pacientes se sintió mejor después de cambiar con las insulinas «Lente».

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Aus der Universitäts-Kinderklinik Würzburg
(Direktor: Prof. Dr. J. Ströder)

Untersuchungen über den Stromaprotein- und Lipoidgehalt von Nabelschnurerythrozyten[1]

von WILHELM KÜNZER

Unser Wissen über das Erythrozyten*stroma* ist im Verhältnis zur Einsicht, welche wir von der Funktion und Struktur des roten Blutfarbstoffes gewonnen haben, noch recht *gering*. Dies ist offenbar vor allem durch die Schwierigkeit bedingt, welche der Gewinnung und Untersuchung eines mengenmäßig genügenden, chemisch reinen Ausgangsproduktes entgegensteht.

Zur Erweiterung der bisherigen Erkenntnisse haben wir die chemische Zusammensetzung von *Nabelschnur-* und *Erwachsenenerythrozytenstromata* untersucht. Derartige *vergleichende* Untersuchungen erschienen hauptsächlich deshalb von Interesse, weil der Nabelschnurerythrozyt nicht das gleiche wie der Erwachsenenerythrozyt ist, sondern sich vor allem in bezug auf die äußere Gestalt, Art des in der Zelle vorhandenen Blutfarbstoffes, Aktivität der zellulären Fermentsysteme und Überlebensdauer davon unterscheidet (3). Es lag daher die Annahme nahe, daß auch die *Membran* des Nabelschnurerythrozyten Abweichungen von derjenigen des Erwachsenenerythrozyten aufweisen würde.

Seiner chemischen Zusammensetzung nach setzt sich das Erythrozytenstroma hauptsächlich aus einem wasserlöslichen Eiweißkörper und einem Lipoidgemisch zusammen, welches Cholesterin, Cholesterinester, Phosphatide und Cerebroside enthält. Unsere Untersuchungen befassen sich mit der Bestimmung des Protein-, Gesamtcholesterin-, Phosphorlipoid- und Eisengehaltes des Stromas von Nabelschnur- und Erwachsenenerythrozyten. Methodisch lehnten wir uns dabei eng an das Vorgehen von Tishkoff, Robscheit-Robbins und Whipple (7) an.

[1] Mit Unterstützung der Deutschen Forschungsgemeinschaft.

Methode

1. *Stromatagewinnung*

Zur Verwendung kamen jeweils 12 cm³ Nabelvenenblut bzw. Venenblut von Erwachsenen, welches mit Heparin (Liquemin-Roche) ungerinnbar gemacht und anschließend sofort weiterverarbeitet oder kurzfristig im Kühlschrank aufbewahrt wurde. Alle Arbeitsgänge erfolgten bei Eisschranktemperatur.

Das Blut wurde durch mehrschichtige Gaze gegeben und auf der Kühlzentrifuge mit 3000 Touren 15 min lang geschleudert. Das Plasma kam mitsamt oberster Zellschicht durch Absaugen zur Entfernung. Der Erythrozytenbrei wurde in Zentrifugengläser gegeben und mit kalter physiologischer Kochsalzlösung mehrmals auf der Kühlzentrifuge gewaschen.

Vom gewaschenen Erythrozytenbrei kamen zweimal 2,0 cm³ in kleine Erlenmeyerkolben. In diesen erfolgte die Hämolyse mittels 10 cm³ Aqua dest., das im Eisschrank 10 min lang auf die Zellen einwirkte. Mit kaltem, 0,2 m Azetatpuffer vom pH 4,6 wurde das Ganze in einen Meßzylinder von 250 cm³ übergespült, der bis zur Marke 150 gefüllt für 5–6 Stunden in den Eisschrank kam. Danach hatten sich die Stromata unter die Marke 100 abgesenkt. Die überstehende stromafreie Hämoglobinlösung wurde dann abgesaugt, die Stromasuspension mit verdünntem Eisessig erneut auf 150 cm³ aufgefüllt. Anschließend kamen die Zylinder wieder in den Eisschrank. Nachdem sich die Stromata unter die Marke 50 abgesenkt hatten, wurde die überstehende Flüssigkeit durch Absaugen entfernt. Die Stromata aber kamen quantitativ in Zentrifugengläser, worin sie mit verdünntem Eisessig (1:10000) auf der Kühlzentrifuge (20000 Touren) gewaschen wurden bis die überstehende Flüssigkeit völlig klar war.

2. *Gesamtlipoidbestimmung*

Die so enthämoglobinisierten Stromata kamen zur Extraktion in 250 cm³ fassende Erlenmeyerkolben, in deren Hals ein Kühlfinger befestigt war. Extrahiert wurde auf dem Wasserbad von 70°C und zwar zweimal 2 Stunden lang mit 60–80 cm³ Alkohol–Äther (3:1) und einmal 1 Stunde lang mit 60–80 cm³ Chloroform–Methanol (1:1). Nach jeder Extraktion wurde abgewartet bis sich die Stromata gut am Boden des Kolbens abgesetzt hatten. Jedesmal wurden die überstehenden Flüssigkeiten in einen etwa 250 cm³ fassenden Schliffkolben dekantiert und dort vereinigt. Im Anschluß an die letzte Extraktion kamen die Stromata auf eine mit stickstoffreiem Filterpapier belegte Nutsche, wo sie zwei- bis dreimal mit 5 cm³ Chloroform–Methanol (1:1) gewaschen wurden. Die Waschflüssigkeiten kamen ebenfalls in den Schliffkolben, während die Stromata zur Bestimmung des Gesamtproteins dienten.

Aus dem Schliffkolben wurde das Alkohol–Äther–Chloroform–Methanol-Gemisch in eine Vakuum-Destillationsapparatur gegeben und bei 70°C unter Einleiten von Stickstoff eingedampft. Aufnahme der Trockenen und Überführung in einen Schütteltrichter von 100 cm³ erfolgte mit 20–25 cm³ leicht erwärmtem Petroläther–Chloroform (6:1). Nach Zugabe von 20–25 cm³ 50%igem kochsalzgesättigtem Alkohol wurde einige Minuten lang geschüttelt und danach die untere Flüssigkeitsschicht in einen zweiten Schütteltrichter von 100 cm³ abgelassen. In diesem wurde mit 40–50 cm³ Petroläther–Chloroform (6:1) erneut einige Minuten lang geschüttelt und dann die untere Flüssigkeitsschicht verworfen. Die obere Flüssigkeitsschicht aus beiden Schütteltrichtern kam dagegen in einen gewogenen, 50 cm³ fassenden Schliffrundkolben zur

Eindampfung im Vakuum bei 70°C unter Stickstoffzufuhr. Anschließend wurde der Rundkolben in den Exsikkator verbracht. Nach Trocknung bis zur Gewichtskonstanz erfolgte Feststellung der Gewichtszunahme des Rundkolbens.

Zur Bestimmung der Phosphorlipoide und des Gesamtcholesterins wurde der Bodensatz in 50,0 cm³ Chloroform aufgenommen.

3. *Phosphorlipoidbestimmung*

10,0 cm³ der Chloroformlösung wurden in einen Kjeldahlkolben gegeben und im Wasserbad eingedampft. Der weitere Arbeitsgang erfolgte nach den Angaben in der Anleitung zum Photometer „Eppendorf" 1956. Stets wurden Doppelbestimmungen gemacht.

4. *Gesamtcholesterinbestimmung*

5,0 cm³ der Chloroformlösung wurden zu diesem Zweck nach den Angaben von Rappaport und Engelberg (5) verarbeitet. Stets kamen Doppelbestimmungen zur Ausführung.

5. *Gesamtproteinbestimmung*

Diese erfolgte in den extrahierten Stromata mittels des Mikro-Kjeldahl-Verfahrens. Zur Umrechnung wurde der Stickstoffgehalt der Proben mit dem Faktor 6,25 multipliziert. Stets erfolgten Doppelbestimmungen.

6. *Gesamteisenbestimmung*

Hierzu wurden Stromata verwendet, die wir aus 2,0 cm³ Erythrozytenbrei nach den unter 1 und 2 niedergelegten Vorschriften gewannen. Der Eisengehalt dieser Proben wurde nach dem Verfahren von Borei (1) in Doppelbestimmungen festgestellt.

Auf eine Diskussion der unter 1 und 2 geschilderten Methoden wurde verzichtet. Die in diesem Zusammenhang wichtigen Fragen haben Tishkoff, Robscheit-Robbins und Whipple (7) geprüft, worauf wir ausdrücklich verweisen.

Ergebnisse und Diskussion

Unsere Resultate sind in den Tab. 1 und 2 aufgezeichnet. Sie enthalten für je 10 Stromaproben aus Nabelschnur- und Erwachsenenblut Doppelbestimmungen des Gesamtprotein-, Gesamtcholesterin-, Phosphorlipoid- und Eisengehaltes. Alle Werte beziehen sich auf 1,0 cm³ Erythrozytenbrei. Für die Nabelschnurerythrozytenstromata ergeben sich folgende Mittelwerte: Gesamtprotein 7,6 mg, Gesamtcholesterin 1,2 mg, Phosphorlipoid 1,6 mg und Eisen 7,4 γ. Für die Erwachsenenerythrozytenstromata lauten die Mittelwerte: Gesamtprotein 7,4 mg, Gesamtcholesterin 1,1 mg, Phosphorlipoid 1,4 mg und Eisen 8,1 γ.

In einzelnen Fällen (z. B. Lab. 1. Nr. 3.: Protein und Phosphorlipoid zeigen die Doppelanalysen ziemlich grosse Differenzen. Dies hängt offenbar mit Substanzverlusten zusammen, welche im Verlauf der langwierigen Präparation gelegentlich auftreten können.

Unsere Ergebnisse zeigen also, daß die *Stromata von Nabelschnur- und Er-*

TABELLE 1

Zusammensetzung der Stromata von Nabelschnurerythrozyten.

Nr.	Gesamtprotein in mg/cm³ Erythrozytenbrei	Gesamtcholesterin in mg/cm³ Erythrozytenbrei	Phosphorlipoid in mg/cm³ Erythrozytenbrei	Eisen in γ/cm³ Erythrozytenbrei
1	7,96	1,26	1,70	4,5
	7,30	1,22	1,80	5,6
2	7,70	1,10	1,80	3,9
	8,40	1,10	1,50	4,6
3	5,80	1,08	1,40	8,5
	9,60	1,47	2,50	7,1
4	8,07	1,20	1,70	7,8
	7,51	1,10	1,30	9,9
5	8,10	1,30	1,60	6,4
	7,80	1,20	1,40	7,1
6	6,34	0,97	1,30	6,2
	6,34	0,96	1,40	7,0
7	6,80	1,10	1,70	9,0
	7,80	1,01	1,50	7,6
8	8,00	1,20	1,10	5,0
	8,70	1,06	1,15	9,5
9	6,90	1,40	1,50	14,0
	8,60	1,40	1,77	11,3
10	6,78	1,97	1,64	5,6
	7,02	1,09	1,54	6,6
Mittelwert:	$7,6 \pm 0,9$	$1,2 \pm 0,15$	$1,6 \pm 0,3$	$7,4 \pm 2,5$

wachsenenerythrozyten praktisch den gleichen Gesamtprotein-, Gesamtcholesterin- und Eisengehalt haben, wenn die Werte auf die Volumeneinheit Erythrozytenbrei berechnet werden. Eine geringfügige Differenz scheint nur hinsichtlich des *Phosphorlipoid*gehaltes zu bestehen. Auf Grund der statistischen Berechnung wird jedenfalls ein diesbezüglicher Unterschied zwischen Nabelschnur- und Erwachsenenerythrozytenstromata wahrscheinlich gemacht. Es muß aber beachtet werden, daß sich dieses Bild bei Bezug der Werte auf eine bestimmte *Zahl* von Erythrozyten erheblich verändern würde. Da Nabelschnurerythrozyten ein wesentlich größeres mittleres Einzelvolumen besitzen als Erwachsenenerythrozyten, sind in der Volumeneinheit Erythrozytenbrei erheblich weniger Nabelschnurerythrozyten als Erwachsenenerythrozyten vorhanden. Auf das *Stroma eines einzelnen Nabelschnurerythrozyten würde also bei Zugrundelegung unserer Werte eine deutlich größere Gesamtprotein-, Gesamtcholesterin- und Eisenmenge entfallen als auf das Stroma eines einzelnen Erwachsenenerythrozyten.*

TABELLE 2

Zusammensetzung der Stromata von Erwachsenenerythrozyten.

Nr.	Gesamtprotein in mg/cm³ Erythrozytenbrei	Gesamtcholesterin in mg/cm³ Erythrozytenbrei	Phosphorlipoid in mg/cm³ Erythrozytenbrei	Eisen in γ/cm³ Erythrozytenbrei
1	6,85	1,30	1,77	9,5
	7,39	1,20	0,83	9,0
2	9,10	1,22	1,58	7,5
	10,50	1,39	1,30	6,6
3	8,66	1,43	0,63	10,8
	9,59	1,71	1,22	11,3
4	8,03	1,30	1,37	8,1
	7,40	1,20	1,52	9,0
5	6,10	0,95	1,50	8,0
	–	–	–	7,6
6	7,35	1,17	1,30	7,2
	6,34	0,86	1,45	7,1
7	6,39	0,96	1,58	6,3
	6,40	0,63	1,15	5,6
8	7,70	1,08	1,27	7,6
	7,43	0,97	1,21	7,3
9	5,99	0,97	1,90	8,3
	5,99	0,96	1,95	6,6
10	6,46	0,94	1,69	9,2
	6,45	0,99	1,25	8,8
Mittelwert:	$7{,}4 \pm 1{,}1$	$1{,}1 \pm 0{,}7$	$1{,}4 \pm 0{,}3$	$8{,}1 \pm 1{,}5$

In der Literatur liegen Untersuchungen über die chemische Zusammensetzung der Nabelschnurerythrozytenstromata nicht vor. Lediglich Zarikoglu (9) hat soeben Bestimmungen bekanntgegeben, denen zufolge die Menge des auf den einzelnen Erythrozyten entfallenen Stromaeiweißes bei Nabelschnurzellen eineinhalbmal größer ist als bei Erwachsenenzellen. Auch den Lipoidgehalt des einzelnen Nabelschnurerythrozyten fand er höher gelegen als denjenigen des einzelnen Erwachsenenerythrozyten. Leider sind diese Werte nicht ohne weiteres mit unseren Ergebnissen vergleichbar, weil die einen auf den einzelnen Erythrozyten, die anderen auf die Volumeneinheit Erythrozytenbrei bezogen wurden. Trotzdem kann festgestellt werden, daß beide Untersuchungen prinzipiell übereinstimmende Aussagen über die chemische Zusammensetzung von Nabelschnurerythrozyten- und Erwachsenenerythrozytenstromata zulassen.

Bei älteren Kindern ist der Lipoidgehalt der Erythrozyten von Erickson, Williams, Hummel und Macy (2) bestimmt worden. Bei 8 gesunden Kindern

im Alter von 5–9 Jahren fanden sie den Gesamtcholesteringehalt im Mittel zu 119 mg/100 g Erythrozytenbrei. Bei Kleinkindern, die im Augenblick der Untersuchung gesund waren, jedoch davor verschiedene Krankheiten durchgemacht hatten, traten keine nennenswerten Abweichungen zutage. Von Schäfer (6) liegen im Rahmen einer experimentellen Studie über die Bedeutung des Cholesterinstoffwechsels für die Genese hämolytischer Erkrankungen ebenfalls Gesamtcholesterinbestimmungen für Erythrozyten von gesunden Kindern jenseits des 4. Lebensjahres vor. Das Gesamtcholesterin in den Erythrozyten der 10 untersuchten Kinder machte im Mittel 108 mg/100 cm^3 Erythrozytenbrei aus. Die Ergebnisse dieser beiden Untersuchungen zeigen also keine bedeutenden Abweichungen von unseren Werten. Etwas höher als bei uns liegt hingegen der Phosphorlipoidgehalt der Erythrozyten in den schon oben genannten Untersuchungen Erickson, Williams, Hummel und Macy (2). Bei den 8 gesunden Kindern im Alter von 5–9 Jahren ergab er sich im Mittel zu 241 mg/100 g Erythrozytenbrei.

Unsere Ergebnisse stimmen im übrigen auch ausgezeichnet mit denjenigen überein, welche Tishkoff, Robscheit-Robbins und Whipple (7) für Stromata von Hundeerythrozyten fanden. Das gleiche gilt für die Untersuchungen von Williams, Erickson, Beach und Macy (8) sowie Parpart und Dziemian (4), die sich ebenfalls mit der chemischen Zusammensetzung der Stromata von Hundeerythrozyten beschäftigten.

Unsicher bleibt vorerst noch, woher das Eisen in unseren Stromata stammt. Da die Bestimmung des Hämoglobingehaltes, welche wir an dreien unserer Stromaproben nach völliger Hämolyse mit Digitonin durchführten, ganz ausserordentlich niedrige Werte ergab, kann es sich nicht allein um eine Verunreinigung mit Hämoglobin handeln. Einstweilen ist aber nicht zu entscheiden, ob das Eisen schon primär in den Stromata anwesend war, also ein essentieller Bestandteil der Stromata ist, oder nach der Hämolyse durch Absorption von Eisen aus den umgebenden Medien eingelagert wurde. In den Untersuchungen von Tishkoff, Robscheit-Robbins und Whipple (7) betrug der Eisengehalt der Stromata etwa 8 γ/cm^3 Erythrozytenbrei, was gut mit unseren Werten übereinstimmt.

Zum Abschluss sei hervorgehoben, dass unsere Untersuchungen keine Aussage über die Feinstruktur der Erythrozytenmembran ermöglichen. An sich sind Differenzen im Feinbau zwischen den Stromaten aus Nabelschnur- und Erwachsenenerythrozyten durchaus denkbar, obgleich sich grobchemisch keine gesicherten Unterschiede ergaben.

Zusammenfassung

Der Gesamtprotein-, Gesamtcholesterin-, Phosphorlipoid- und Eisengehalt werden an je 10 Stromaproben aus Nabelschnur- und Erwachsenenblut bestimmt. Bei Bezug auf 1,0 cm³ Erythrozytenbrei weisen die erhaltenen Werte für Nabelschnurerythrocytenstromata von denjenigen für Erwachsenenerythrozytenstromata keine gesicherten Unterschiede auf.

Investigations into the stromal protein and lipid level of erythrocytes in the umbilical cord.

The total protein, total cholesterol, phospholipid and iron levels were determined each in 10 stromal samples of umbilical cord and adult blood. The values obtained per 1.0 ml erythrocyte pulp showed no definite difference between umbilical-cord erythrocyte stromata and adult erythrocyte stromata.

Recherches sur la teneur du stroma des érythrocytes du cordon ombilical en protéines et en lipides.

Des déterminations du taux des protéines totales, du cholestérol total, des phospholipides et du fer ont été effectuées sur 10 échantillons de stroma provenant de sang prélevé dans des cordons ombilicaux ainsi que sur 10 échantillons de sang prélevés sur des personnes adultes. Par cm³ de pâte d'érythrocytes, les valeurs obtenues pour les stromas d'érythrocytes provenant de cordons ombilicaux ne s'écartèrent pas sensiblement de celles qui furent trouvées pour les stromas d'érythrocytes provenant du sang de personnes adultes.

Investigaciones sobre el contenido proteico y lipoídico del estroma de los hematíes del cordón umbilical.

Se ha determinado el contenido en proteinas totales, colesterina total, fosfolípidos y hierro en 10 muestras de sangre procedente de cordón umbilical y de sujetos adultos. Los valores obtenidos para el estroma de los hematíes procedentes de cordón umbilical, en relación a 1 cc. de papilla de hematies, no presentan ninguna diferencia significativa con el estroma de los hematies del adulto.

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Würzburg,
Universitäts-Kinderklinik

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and Statens Serum Institut. (Chief: J. Ørskov, M.D.)

Serum Protein Values in Premature Infants

Paper-electrophoresis

by F. TUDVAD, A. BIRCH-ANDERSEN, and I. L. MARNER

The value of protein-rich diets to premature infants has been discussed in several papers (Levine & Gordon (1942), Magnusson (1945), Lind (1945), Rothe-Meyer (1949), Young *et al.* (1950), Crosse *et al.* (1954)), in which such diets were found to accelerate increases of weight more than human milk and the generally used milk-mixtures. However, it is rather doubtful whether this accelerated gain of weight is desirable since a development of detrimental secondary effects of the protein-rich milk mixtures cannot be precluded.

Some investigations give certain evidence to this effect. The faint inclination towards the development of acidosis, which is a well known feature in normal, premature infants, has been found to be accentuated after protein-rich diets (Darrow (1945), Dupont (1948)). Rothe-Meyer (1949) found blood urea values in premature infants fed on half-skimmed citric acid milk about twice as high as the values found in premature infants fed on human milk.

Crosse *et al.* (1954) found a lower frequency of infection in premature infants fed on human milk than in infants fed on human milk with additional protein; the haemoglobin figures were also higher in the former than in the latter group. Besides this, the incidence of slight rickets was highest in the latter group. Although the weights registered by Crosse *et al.* demonstrate how the highest increase is found in infants fed on half-skimmed dried milk, it must be admitted that infants fed on human milk had gained most in weight at the age of six months.

Several authors have examined the serum protein values in premature infants, e.g. Darrow & Cary (1933) who found total protein values up to 4.9 g per cent, Hickmans *et al.* (1943) who during the first four weeks of life in premature infants found total protein values ranging between 3.7 and 5.4 g per cent; McMurray *et al.* (1948) found total serum protein values

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during the first week of life in premature infants at 5.6 ± 0.47 g per cent, serum albumin values at 4.3 ± 0.60 g per cent, and globulin values at 1.6 ± 0.37 g per cent. Rothe-Meyer (1949) has shown that premature infants fed on half-skimmed citric acid milk developed higher concentrations of serum proteins than premature infants fed on human milk. In either group a decline in total protein values was evident from the age of 0–10 days and up to the age of 36–65 days. A fall in total protein values was registered, viz. in infants fed on human milk from 4.77 to 4.17 g per cent, and in infants fed on citric acid milk from 5.29 to 4.60 g per cent. This fall must be considered due mainly to a fall in the globulin values (from 1.51 to 0.95 g per cent in infants fed on human milk, and from 1.63 to 1.14 g per cent in infants fed on half-skimmed citric acid milk), whereas serum albumin remained rather constant during the experimental period. Later Rothe-Meyer (1956) found that human milk with additional protein (a casein preparation Seccosan) and half-skimmed citric acid milk gave identical serum protein values. Norton *et al.* (1952) registered a gradual fall in total serum protein values in premature infants, viz. from about 6 g per cent at birth to about 4.5 g per cent at the age of 30 days, however, without demonstrating any definite relation to the birth weight. Electrophoretic fractionation of the proteins showed a similar decrease in the serum albumin values, whereas alpha$_1$, alpha$_2$, and beta-globulin values showed marked fluctuations. However, a definite decrease was registered in the gamma-globulin values viz. from 0.7 g per cent at birth to 0.2 g per cent at the age of 40 days.

Scatter diagrams prepared by Young *et al.* (1950) record the total protein values in premature infants between about 3.2 and 5.7 g per cent within the first two weeks of life and slightly decreasing during the first five or six weeks of life, particularly so in such premature infants as showed the lowest birth weights. During the first two weeks of life serum albumin values ranged between 2.7 and 4.1 g per cent, but the diagrams seem to indicate a certain rise during the first 12 weeks of life. At the age of two weeks the globulin values ranged between 0.6 and 2.8 g per cent; the diagrams seem to indicate a slight decrease, occurring during the first weeks of life and followed by a slight rise with age up to the age of 12 weeks. Any definite interrelation of diets and serum proteins could not be found in the biggest of the premature infants, whereas the serum protein values in the smallest of the premature infants seemed to be somewhat higher in those fed on the most protein-rich diets.

Crosse *et al.* (1954) give no serum protein values but state merely that "they showed the same wide scatter as was found by Young *et al.* (1950)". These authors find that the smaller the premature infants were and the less mature, the lower were the serum protein concentrations, and in addition to

this that a fall in total protein values was evident in all premature infants during the first six to eight weeks of life. Only in premature infants with birth weights between 1134 and 1361 g was a certain interrelation demonstrable between diets and serum protein values, and the lowest protein values were found after administration of dried milk and human milk to which protein was added. Serum albumin showed the same fall and rise as the total protein, whereas the globulin concentration which was low at birth remained at the same level without any particular relation to the diet.

Unless otherwise stated the papers referred to in the above include only determinations of the total serum protein values and separation by salting out of total albumin and total globulin.

Although several papers are available in which the problem of serum protein values in premature infants is discussed, the question cannot be considered fully elucidated, particularly not if consideration be paid to recent years' technical advances in the field of differentiation of protein fractions by means of electrophoresis.

The *object of the present paper* is (1) to determine the various serum protein fractions in premature infants fed on human milk, and (2) to examine whether or not serum proteins are affected by the addition of protein to human milk.

Own Material

The examination includes 21 premature infants whose birth weights ranged between 1500 and 2400 g; throughout the experiment (about eight weeks) the infants received human milk; later in the experiment 10 of the babies received additional protein in the form of Seccosan[1] administered in doses of 1.5 g per cent per 100 ml human milk.

Fontanelle punctures were performed on the infants included in the experiment and about 2 ml of blood was drawn into a tapering glass about once a week and centrifugated immediately upon clotting of the blood; the serum was pipetted into glasses which after plugging were stored at − 18°C until an analysis could be performed.

Technique

The paper electrophoresis was performed according to the technique described by Kunkel & Tiselius (1951). Filter paper: Grycksbo-Munktell, no. 150/20. Buffer: Veronal, pH 8,6 $\mu = 0.1$. Electric current: 8 mA for 17 hours. Protein staining in 1 per cent solutions of brome-phenol-blue in alcohol containing 25 per cent of sublimate. The dye not bound to proteins is washed out by 0.5 per cent solutions of acetic acid. After drying the paper is cut into 0.5 cm wide strips at right angles to the direction of migra-

[1] We are informed by the factory "Ferrosan" that Seccosan is produced from skimmed milk acidified by pure lactic acid streptococci cultures. Composition: 89 per cent of pure casein, 1.5 per cent of milk sugar, 1.5 per cent of fat, 3 per cent of ashes, and 5 per cent of water.

tion and each strip is eluted for one or two hours in 5 cc of 0.01 n NaOH. The intensity of the blue colour in each tube is read in a spectrophotometer at a wavelength of 595 mμ. The extinction values of the individual readings are plotted against the corresponding tube-number, and a curve similar to the concentration gradient known from the free electrophoresis is thus obtained. The area under each peak is proportional to the concentration of the represented protein component. The area under each peak is measured by means of a planimeter and the relative concentration of each group calculated as the percentage of the total area of all components.

Knowledge of the total protein concentration in a certain serum and of the relative concentrations of the individual components determined by paper-electrophoresis permits the determination of the "absolute" values of the individual protein groups; it should be pointed out, however, that such "absolute" values are indeed very rough estimates of the actual concentrations because of the relatively high inaccuracy of the paper-electrophoresis method used.

Results

Table 1 records findings from the determinations of the total serum protein values and the various fractions registered in premature infants fed on human milk and human milk plus Seccosan.

It is apparent from Table 1 that total protein values in infants who did not receive additional protein fell during the experimental period from 5.63 g per cent during the first week of life to 4.03 g per cent during the eighth week of life. Human milk with additional protein will increase the total protein values but not prevent the decrease which is concurrent with the decrease in total protein values occurring in infants fed on human milk exclusively (Fig. 1).

TABLE 1

Distribution in percentages of electrophoretically separated serum proteins in premature infants fed on (1) human milk with additional Seccosan (+S) or (2) on human milk (−S) alone.

Age in days	Number of tests		Total protein g %		Gamma-glob. %		Beta-glob. %		Alpha$_2$-glob. %		Alpha$_1$-glob. %		Albumin %	
	+S	−S	+S	−S	+S	−S	+S	−S	+S	−S	+S	−S	+S	−S
0–7	0	10	—	5.63	—	18.2	—	12.0	—	12.2	—	6.6	—	51.1
8–14	1	16	5.80	5.12	17.2	16.8	8.7	10.7	10.9	12.6	5.4	5.4	57.9	54.7
15–21	3	18	5.48	5.10	13.5	16.8	11.4	10.2	11.1	13.9	5.4	5.5	58.6	53.5
22–28	4	17	5.28	5.05	13.6	15.4	13.0	11.8	12.2	13.3	5.8	5.6	55.4	54.0
29–35	7	13	5.19	4.81	11.2	15.0	12.3	10.5	12.8	14.0	5.3	5.8	58.4	54.5
36–42	8	10	4.99	4.48	11.1	14.8	11.5	10.8	12.9	14.5	5.0	5.9	59.7	54.1
43–49	7	4	4.93	4.48	10.8	16.1	12.6	9.9	14.7	13.7	6.3	6.5	55.6	54.0
50–56	5	1	4.79	4.03	9.0	12.9	12.9	9.6	14.1	14.9	6.2	6.0	58.0	56.7

Medföljer som tidningsbilaga

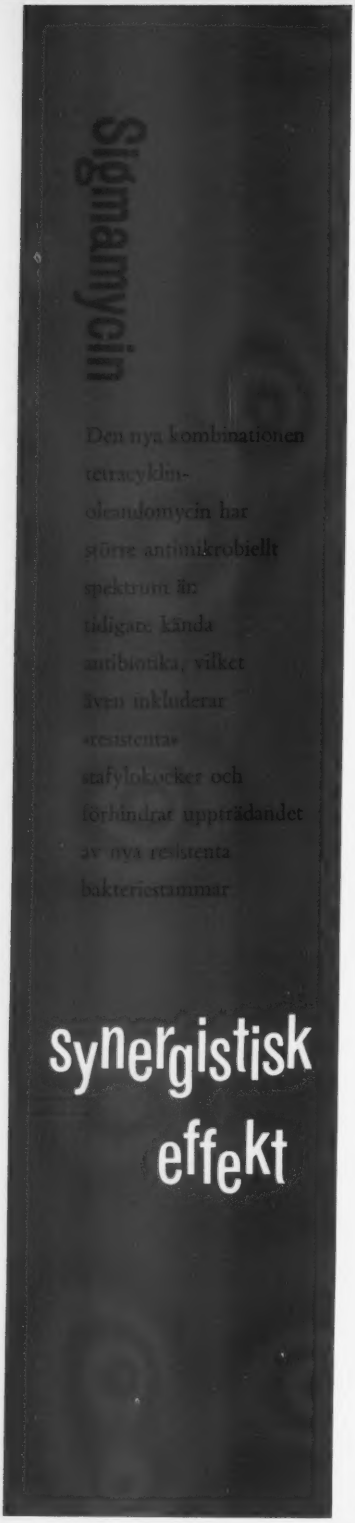
PFIZER, upptäckaren av tetracyklinet, fortsätter som banbrytare inom utvecklingen av livsräddande antibiotika.
En ny antimikrobiell substans, oleandomycin har upptäckts, vilken i kombination med tetracyklin löser resistensproblemet i samband med behandling med bredspektrum-antibiotika.
Namnet på denna kombination är

Sigmamycin

oleandomycin tetracyklin

Sigmamycin är verksamt mot många stafylokockstammar och andra bakterier, som förvärvat resistens mot övriga bredspektrum-antibiotika. Sigmamycin fördröjer utvecklingen av nya resistenta stammar. Sigmamycin har genom kombinationen oleandomycin/tetracyklin en utpräglat synergistisk verkan.

Pfizer



tetracyklin

Den synergistiska effekten påvisad in vitro mot antibiotika-resistenta stafylokocker*

oleandomycin

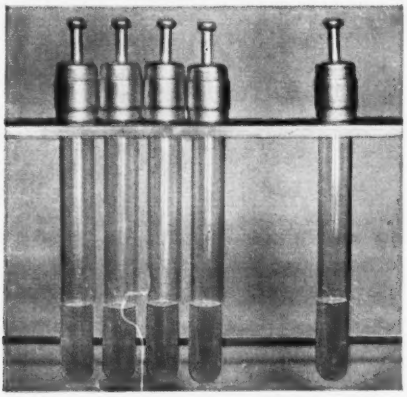
ett nytt Pfizer-antibiotikum

Sigmamycin

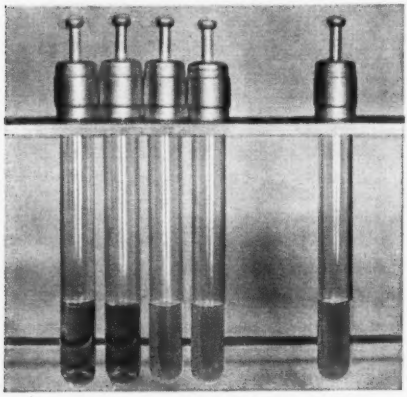
synergistiskt verkande kombination av tetracyklin och oleandomycin

* *Successivt minskade mängder av antibiotikum har satts till en serie rör innehållande konstant mängd buljong. Varje rör ympas med en konstant mängd av den standardkultur, som prövas, i detta fall stafylokocker. Den minsta mängden antibiotikum, som hämmar växten och således ger en klar, ej av bakterier grumlad buljong, anger bakteriens känslighet för antibiotikum.*

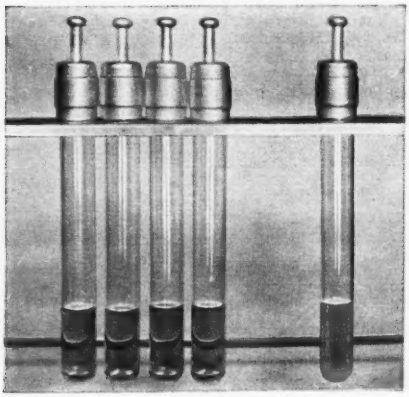
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1433



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten

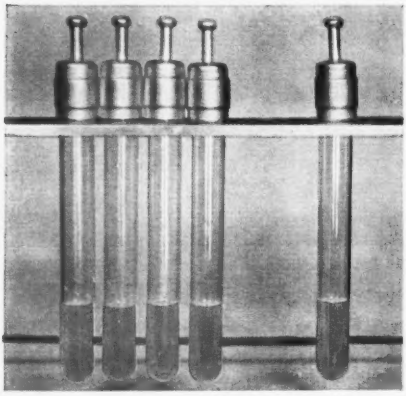


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 2.5 γ/ml

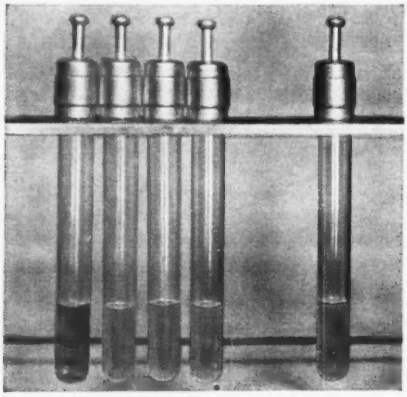


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

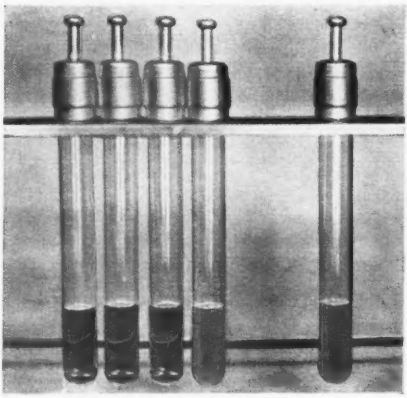
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1457



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten

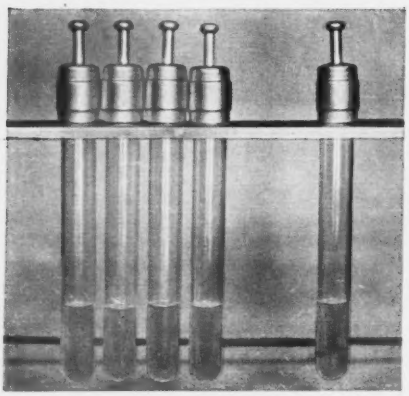


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 5.0 γ/ml

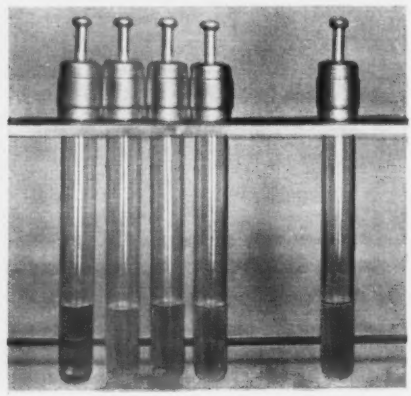


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning vid 1.25 γ/ml

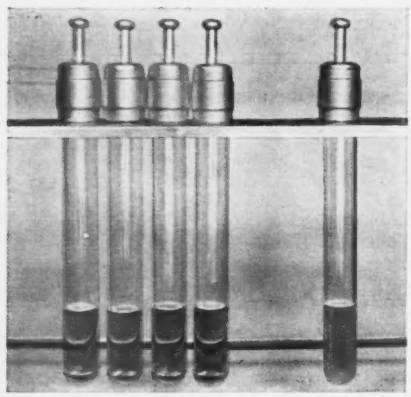
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. aureus No. 1475



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten

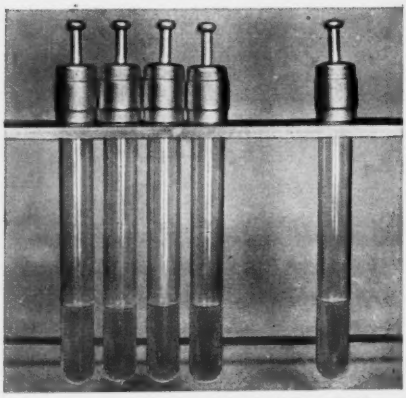


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 5.0 γ/ml

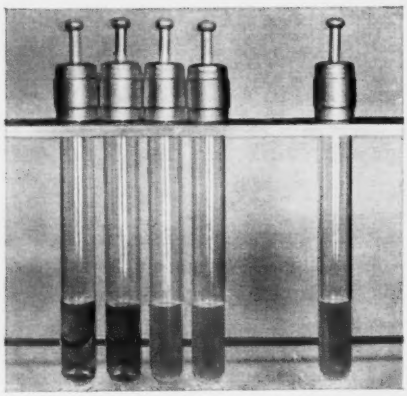


Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

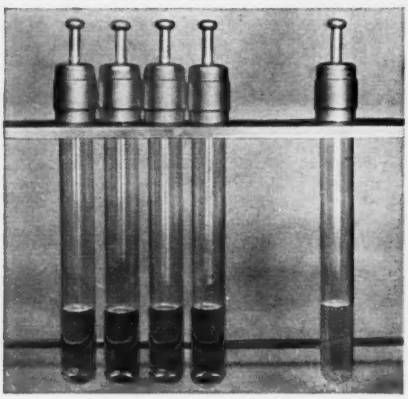
Antibiotika-resistenta bakteriekulturer av M. pyogenes var. No. NB 17



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
tetracyklin: ingen hämning av bakterieväxten



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
oleandomycin: hämning vid 2.5 γ/ml



Konc. 5.0 2.5 1.25 0.625 γ/ml Kontroll
Sigmamycin: hämning i alla spädningar

Sigmamycin

oleandomycin tetracyklin

Tetracyklin och oleandomycin förstärker varandras verkan.
Denna synergistiska effekt visar sig bl. a. i god verkan på
stafylokocker och streptokocker. Den fördröjer vidare uppkomsten
av antibiotika-resistenta sådana bakterier.
Försök in vitro och in vivo visar god effekt såväl mot stafylokocker
som streptokocker, som är resistenta mot andra antibiotika.
Lämpligt för behandling av patienter, hos vilka bredspektrumbehandling
är nödvändig och då resistensprövning är svår att genomföra.

Pfizer

Pfizer

Indikationer — Samma som för andra bredspektrum-antibiotika, omfattande infektionssjukdomar, orsakade av ett stort antal mikroorganismer. Dessa omfattar grampositiva och gramnegativa (aeroba och anaeroba) bakterier, rickettsier, spirocheter, stora virus, protozoer och vissa maskar.

Sigmamycin

oleandomycin tetracyklin

Dosering — *Vuxna:* 1 kapsel var 6:e timme. Vid svårare infektioner 2 kapslar var 6:e timme.
Större barn: Samma dosering som för vuxna.
Spädbarn och småbarn: 10—20 mg per kg kroppsvikt och dag. Vid svårare infektioner 20—40 mg per kg kroppsvikt och dag. Dagsdosen fördelas på 4 enkeldoser.
Sigmamycin absorberas lätt och adekvata serumkoncentrationer nås hastigt. Fördragbarheten är god och sådana biverkningar, som ses vid användning av andra bredspektrum-antibiotika ses sällan med Sigmamycin.

Förpackningar — Kapslar à 250 mg. Varje kapsel innehåller 83 mg oleandomycin och 167 mg tetracyklin. Glas à 16 och 100 kapslar.

PFIZER AKTIEBOLAG, STOCKHOLM Ö

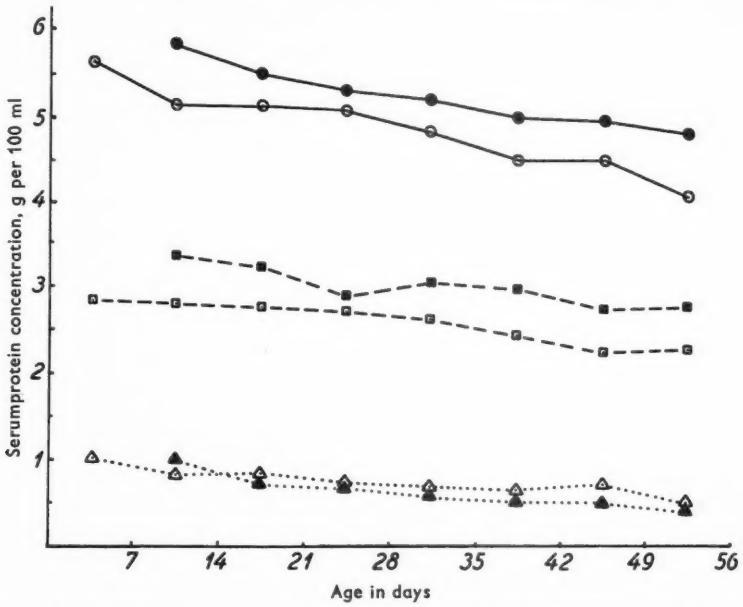


Fig. 1. Total proteins (○——○), albumins(□----□), and gamma-globulins (△ ..... △) as related to age in premature infants. Non-hatched symbols refer to premature infants fed on human milk, hatched symbols refer to premature infants fed on human milk with additional protein (Seccosan).

Alpha$_1$, alpha$_2$, and beta-globulins remain rather constant and uniform throughout the experimental period, whereas a pronounced decrease is evident in the gamma globulin values viz. from about 1 g per cent during the first week of life to about 0.5 g per cent during the eighth week of life. Additional Seccosan causes a further decrease in the gamma-globulin values which are about 0.1 g per cent lower in infants who received additional Seccosan than in those to whom it was not administered.

A fall from a little less than 3 g per cent during the first week of life to a little above 2 g per cent during the eighth week of life was also manifest in the albumin values. After addition of Seccosan the albumin values would remain at higher levels whereas the actual decrease in the values would be identical in either group.

Discussion

Our findings of total protein concentrations during the first week of life (average 5.63 g per cent) is in fair accordance with findings in premature infants by McMurray *et al.* (1948) and Norton *et al.* (1952), but is rather

higher than reported by Darrow & Cary (1933), Hickmans *et al.* (1943), Rothe-Meyer (1949), Young *et al.* (1950), Crosse *et al.* (1954). If compared with total protein values in full-term infants (Longworth *et al.* (1945), McMurray *et al.* (1948), Knapp & Routh (1949), Orlandini *et al.* (1955)) it will be noted that the total serum protein values are much lower in premature infants.

In conformity with Rothe-Meyer (1949) we find that higher protein contents in the diet will produce a rise in the total serum protein values and that the total protein amount is decreasing during the first month of life. This finding is also substantiated by Norton *et al.* (1952) and Crosse *et al.* (1954). However, it is still open to discussion which protein groups are actually involved in this decrease. Rothe-Meyer (1949) found e.g. that albumin values remain unchanged and that the fall is due mainly to a decrease in total globulin values, which is also apparent from the diagram of Young *et al.* (1950), whereas Norton *et al.* (1952) and Crosse *et al.* (1954) found identical decreases in albumin and protein values.

In our opinion the decrease in total protein values is due to falls both in albumin and globulin values. But the decrease in gamma-globulin values is less pronounced than stated by Norton *et al.* (1952) and Orlandini *et al.* (1952) who examined premature and full-term infants, respectively.

Some of the above discrepancies may certainly be explained as results of the variations in the applied techniques; most investigators e.g. have confined themselves to determinations of the total globulin values. The different diets and durations of investigations may form another source of errors e.g. because increased protein contents in the diet will give higher total protein values (albumin) and increasing age will produce a decrease in total protein values ascribable to decreases in the albumin and gamma-globulin fractions.

The decrease in gamma-globulin values, which is concurrent with increasing age, observed in the present investigation, together with the fact that gamma-globulin values will decrease further if casein be added to human milk, seem to us to be of some importance since antibodies are known to be of a gamma-globulin character.

Summary

In 21 premature infants, the birth weights of whom ranged between 1500 and 2400 g and the ages between 1 and 56 days, the total serum protein values have been determined and the serum protein components have been electrophoretically differentiated. All infants were fed on human milk but, in 10 infants additional protein was administered (Casein preparation *Seccosan*).

Total protein values were found to be lower in premature infants than in full-term infants. During the first eight weeks of life total protein values decreased from 5.63 g

per cent to 4.03 g per cent. The decrease in total protein is caused by a decrease in the amount of albumin (from a little below 3 g per cent in the first week of life to a little above 2 g per cent in the eighth week) and of gamma-globulin (from about 1 g per cent to about 0.5 g per cent) while the alpha$_1$-, alpha$_2$- and beta-globulin values remain rather constant. If casein is added to the diet the total serum protein values and the serum albumin values will range at higher levels, but the decrease with increasing age will not be prevented. On the contrary, additional casein to the diet will cause a further reduction in the gamma-globulin concentrations (Fig. 1).

Taux des protéines dans le sérum des prématurés.

Des déterminations du taux des protéines totales ainsi que des taux particuliers des différentes protéines ont été effectuées par électrophorèse chez 21 bébés nés avant terme. Tous ces enfants étaient nourris au lait maternel et 10 d'entre eux reçurent des suppléments de protéines. Il est apparu que le taux des protéines totales était plus faible chez les prématurés que chez les enfants nés à terme. Au cours des huit premières semaines qui suivirent la naissance, le taux des protéines totales descendit de 5,63 g % à 4,03 g %. Cet abaissement du taux des protéines totales provenait de la diminution de la concentration en albumine (qui d'abord légèrement inférieure à 3 g % au cours de la première semaine était descendue à un niveau légèrement supérieur à 2 g % au bout de huit semaines) et en gamma-globuline (qui, étant d'environ 1 g % était descendue à environ 0,5 g %), tandis que les taux des globulines alpha$_1$, alpha$_2$ et bèta étaient restés relativement constants. L'addition de caséine à la nourriture fit monter les taux des protéines totales et de l'albumine à des niveaux plus élevés, mais ces concentrations diminuèrent également avec le temps. D'autre part, l'addition de caséine à la nourriture entraîna une diminution plus importante du taux des gamma-globulines.

Serumproteinwerte bei frühgeborenen Kindern.

Bei 21 frühgeborenen Kindern wurden die gesamten Serumproteinwerte bestimmt und die Serumproteinbestandteile elektrophoretisch differenziert. Alle Kinder wurden mit Frauenmilch ernährt, aber 10 Kinder erhielten einen Eiweisszusatz. Die gesamten Proteinwerte erwiesen sich bei den frühgeborenen Kindern als niedriger als in vollreif geborenen. Während der ersten 8 Lebenswochen fielen die totalen Proteinwerte von 5,63 % auf 4,03 % ab. Der Fall im Gesamtproteingehalt ist durch einen Abfall im Albumingehalt bedingt (von ein wenig unter 3 g % in der ersten Lebenswoche auf ein wenig über 2 g % in der achten Woche) und Gammaglobulingehalt (von ca. 1 g % auf ca. 0,5 g %), während die Alpha$_1$-, Alpha$_2$- und Betaglobulinwerte ziemlich konstant bleiben. Wenn Kasein zur Diät zugefügt wird, werden die gesamten Serumprotein- und Serumalbuminwerte ein höheres Niveau erreichen, aber der mit dem Alter einhergehende Abfall wird nicht verhindert werden. Im Gegenteil, der Kaseinzusatz zur Diät bewirkt eine weitere Herabsetzung der Gammaglobulinkonzentrationen.

Valores seroproteicos en los prematuros.

Han sido determinados, en 21 prematuros, los valores seroproteicos totales y diferenciados electroforéticamente los componentes seroproteicos. Todos los niños fueron alimentados con leche humana, pero a 10 de ellos se les administraron proteínas adicionales. Hallóse que los valores proteicos totales eran inferiores en los prematuros a los de los niños nacidos a término. Durante las ocho primeras semanas de la vida,

los valores proteicos totales disminuyeron de 5.63 g % a 4.03 g %. La disminución del total proteico está causada por una disminución de la cantidad de albúmina (desde un poco menos de 3 g % en la primera semana de la vida hasta un poco más de 2 g % en la octava semana) y de gammaglobulina (desde aproximadamente 1 g % a aproximadamente 0.5 g %) mientras los valores globulínicos alfa$_1$, alfa$_2$ y beta, permanecen bastante constantes. Si se añade caseína a la dieta, los valores seroproteicos totales y los valores seroalbuminosos alcanzarán niveles más elevados, pero la disminución, al aumentar la edad, no podrá evitarse. La caseína, contraria, adicionada a la dieta, causará todavía más reducción en las concentraciones gammaglobulínicas.

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Hypertonic Expansion of the Extracellular Fluids

by R. A. McCANCE and E. M. WIDDOWSON

Given the two following postulates, hypertonic expansion of the extracellular fluids must take place:—

(1) An intake of sodium chloride greater than will be excreted by the kidney and sweat glands until the concentration within the body has risen above the normal limits.

(2) An intake of water greater than that required to maintain the normal volume of extracellular fluids, but insufficient to meet the amounts being excreted by all channels *and* the maintenance of a normal internal concentration of electrolytes.

The object of this paper is to show that it is relatively easy to satisfy these two requirements simultaneously during the newborn period and in early life, and to demonstrate some of the results.

There is no doubt that the syndrome has been produced before this in human infants, but it is not mentioned by McQuarrie (1944), Finberg & Harrison (1955) or by Weil & Wallace (1955). It is known that if chicks are given too much salt in their drinking water they become oedematous (Selye, 1943; Selye & Stone, 1943), and concentrations of chloride well above normal have been found in the serum (Krakower & Goettsch, 1945). The focus of interest in this work, however, was the fact that the large intake of salt caused highly pathological changes in the kidney, and the hypertonic expansion of the extracellular fluids was allowed to pass without comment.

In experiments on the nitrogen metabolism of piglets during the first days of life (McCance & Widdowson, 1956), some of the piglets were given an evaporated cow's milk mixture. This contained more sodium chloride than sow's milk, and piglets having it developed hypertonic oedema. Those experiments, however, were not perfectly controlled for a study of this syndrome, and, moreover, they did not include a study of the effects of salt and water in otherwise starving animals. The present investigation was designed to confirm and extend the previous findings and to study the effects of salt solution with and without food on newborn piglets. Some studies have also been made on human babies.

Experimental Technique

The work has been done on three litters of newborn piglets and three premature infants.

Piglets

The general arrangements were the same as those described by McCance & Widdowson (1956), but there were differences in detail which are given below.

When five piglets of similar size had been born, and had had a little time to dry, they were weighed and put into metabolism cages as in the previous work.

The animals were fed by stomach tube every two hours. The first piglet was given water, the second an equal volume of salted water, the third a volume of sow's milk $\frac{5}{4}$ times larger than the volume of water. This made the intakes of water about equal, since sow's milk contains 15–20 % of solids. The fourth piglet was given a volume of sow's milk equal to that given to the third, and to which salt had been added to make the concentration of sodium chloride in the water of the milk equal to the concentration of salt in the solution used for the second. The fluids administered were warmed, but the exact temperature was seldom measured as it did not seem to matter. The last piglet acted as an additional control and was given no food or water—a treatment now considered highly satisfactory for infants born before term. The experiments lasted for forty hours, and the room temperature varied between 24° and 27°C. Each experiment was self-contained and internally controlled, but in the first the concentration of salt in the water was 0.5 %, in the second 0.7 %, and in the third 0.9 %. Colostrum was used in the second experiment but not in the first or third. These differences were deliberate and the effects instructive, but they make it undesirable to present some of the results as averages of all three experiments.

The urines were collected in three periods of twelve, twelve and sixteen hours and analysed separately. The animals were not killed, as before, by a blow on the head, but by injecting 40 ml of air into the heart without removing the needle through which blood had been withdrawn for analysis. Death appeared to be almost instantaneous, and this technique has proved very satisfactory. Some of the blood was allowed to clot, and heparin was used to prevent coagulation of the remainder. The serum was separated, the heparinised samples set up for haematocrit within an hour-and-a-half, and the organs were removed for analysis as soon as possible. The two openings of the stomach were tied up before the organ was taken out of the body, and the contents were removed and analysed. The amounts of N, Na, K and Cl found in the stomach were deducted from the amounts administered when balancing the intakes and outputs.

The whole of the feeding by stomach tube was done by one person (R. A. M.); it is not always at all easy to do this even when the animals are skilfully held. They may refuse to make any swallowing movements, and either make active movements to extrude the tube, or hold it between the tongue and the roof of the mouth for long periods, but at the same time struggling, jerking and squealing without pause. Gentleness and considerable patience were often required.

Human infants

Three premature babies have been investigated. The first was a girl aged three weeks, and her urine was not collected continuously as it was from the two boys, whose ages were six weeks and two-and-a-half weeks.

Permission to make these tests was always obtained from the parents beforehand. While the children were still in the maternity hospital and were gaining weight steadily on a standardised diet, urine and blood were collected for clearance studies. The blood was collected from the heel, and the serum separated. The length of this fore period varied from a few hours to twenty-three hours. The concentration of salt in the girl's milk was then raised to 0.9 %, and in the boys' milk to 0.7 %, and all the specimens of urine passed by the boys were collected separately and later pooled in appropriate periods for analysis. The babies were weighed every twelve hours, and after what seemed the proper time as judged by the changes in weight and the appearance of the baby, further samples of blood were withdrawn and the normal diet restored. The collection of urine was continued as long as it was thought to be desirable, and a final sample of blood was then collected and the experiment brought to a close. Twelve or twenty-four hourly weighings were continued for several days. One of the babies had one feed of expressed breast milk each day, but its other feeds, and all those of the other two babies, consisted of Ostermilk. The infants were fed three-hourly seven times a day, with one—the 7 a.m.— feed omitted. Salted milk was given to the girl in experiment 1 for thirty-six hours, to the boy in experiment 2 for fifty-eight hours, and to the boy in experiment 3 for thirty-three hours.

Chemical methods

These were all the same as those used in the investigation described by McCance & Widdowson (1956).

Results on the Piglets

Matters of observation

The fact that the animals were fed two-hourly meant that they were frequently inspected and handled throughout the whole experiment. The newborn pig appears to stand up to starvation remarkably well, and the ones given water but no food were lively and fit at the end, and could almost certainly have been reared had arrangements been made for doing so. The one given nothing at all seldom stirred, but lay in its cage for many hours on end and only rose spontaneously to pass urine. The others settled down quietly between feeds, especially if the cages were kept dark, and made little noise unless disturbed. As the experiment progressed, the animals which were being given salt began to look pinker and more flourishing than their controls. Later they became more sluggish and did not move about much till they were disturbed, but they resisted the passage of the stomach tube just as fiercely, and seemed just as strong at all times. By the end of the experiments, particularly of experiments 2 and 3, they were frankly oedematous (Plate 1), although they were still very pink and had lost none of their "bloom".

Quantitative measurements

Table 1 shows the general effects of administering salt on the body weight, haematocrit, and concentrations of urea, creatinine and potassium in the

1 2 3 4

Plate 1. The appearance of the piglets at the conclusion of the second experiment. *1*, water; *2*, salted water; *3*, milk; *4*, salted milk. Numbers 3 and 4 were smaller animals than 1 and 2, but 1 and 2 were nearly the same weight one as the other at birth, and so were 3 and 4.

serum. The results of these observations have been given as averages. The figures indicate that a loss of weight on water alone, or on nothing, was converted to a gain by salt, and that a satisfactory gain of weight on milk, or colostrum and milk, was magnified by the salt, and to roughly the same extent. Haematocrits may vary considerably within one litter, but with this reservation the results go to show that the salt produced some haemodilution. The differences between the haematocrits of the piglets on milk and on water were clear, and due to the food value of the former, but these differences will not be discussed in the present paper. The administration of salt had no adverse effect upon renal function as judged by the serum urea and creatinine and, as will be shown later, there was a real basis for the reductions in the serum values apart from the expansion of the body fluid throughout which the urea may be assumed to have been dissolved. The administration of salt made no consistent difference to the concentration of K in the serum. Table 2 shows the effect of adding progressive amounts of salt to the water and to the milk on the percentage of water in the carcasses, livers and kidneys of the animals at death. The results for the three animals given water, milk and nothing have been averaged. The addition of salt to the water increased progressively the amount of water found in the carcasses, and the same is true of the addition of salt to the milk. The differences between the animals given milk and those given water were

TABLE 1

The effect of adding salt to the water and to the milk administered to piglets on the body weight, haematocrit, and the concentration of urea, creatinine and potassium in the serum.

Fluid administered ...	Water	Salted water	Milk	Salted milk	Nothing
Change of weight g/kg of weight at birth	−53	+96	+68	+192	−75
Haematocrit %	45.1	42.5	33.3	31.4	48.2
Serum urea mg/100 ml	42.2	23.6	21.1	19.6	32.4
Serum creatinine mg/100 ml	1.55	1.61	1.51	1.15	1.17
Serum K m.eq./l	5.03	5.12	5.57	4.60	4.98

TABLE 2

The effect of adding progressive amounts of salt to the water and to the milk on the percentage of water in the carcasses, livers and kidneys of piglets.

(All results expressed as g water per 100 g fresh tissue.)

Fluid administered ...	Water	Salted water			Milk	Salted milk			Nothing
Experiment ...	Average of 3	1	2	3	Average of 3	1	2	3	Average of 3
Carcass % water in	82.7	85.5	86.7	87.4	79.8	82.5	83.3	84.1	82.6
Liver % water in	81.3	82.8	82.3	81.8	78.7	79.6	79.8	78.9	81.5
Kidneys % water in	84.3	85.9	85.2	85.1	83.2	85.6	84.2	84.4	83.9

due to the food value of the milk, and are one of the well known effects of starvation as compared with good nutrition. The animals given nothing contained almost exactly the same percentage of water as those to whom water had been administered. This volume of water alone caused no retention of water in these newborn animals. It might have done so in others, e.g. the rat with less mature renal function. The addition of salt to the water and to the milk also increased the percentage of water found in the livers and kidneys, but to a smaller extent, and there is a suggestion that the larger the amount of salt added the less the effect upon the percentage of water. The explanation offered for these findings is that the cellular organs accom-

TABLE 3

The effects of adding progressive amounts of salt to the water and to the milk administered to piglets on the volume of urine, the visible water balance, the Na and Cl balances and the concentrations of Na and Cl in the serum.

(All results for intakes and excretions expressed per kg weight at birth per 24 h.)

Fluid administered ...	Water	Salted water			Milk			Salted milk		
Experiment ...	Average of 3	1	2	3	1	2	3	1	2	3
Water intake, ml	247	227	245	251	248	285	294	261	290	274
Urine vol., ml	247	119	101	58	175	180	219	86	62	67
Visible water balance, ml	±0	+108	+144	+193	+73	+105	+75	+175	+228	+207
Na intake, m.eq.	0	20.6	28.6	39.0	2.6	6.5	4.6	20.3	34.5	41.7
excretion, m.eq.	0.3	0.4	4.5	3.5	0.3	0.3	0.1	0.7	2.2	6.9
balance, m.eq.	−0.3	+20.2	+24.1	+35.5	+2.3	+6.2	+4.5	+19.6	+32.3	+34.8
Cl intake, m.eq.	0	20.6	28.6	39.0	4.6	6.4	5.8	22.7	36.3	42.8
excretion, m.eq.	1.1	4.3	5.8	4.6	3.3	2.7	3.3	6.6	7.7	14.6
balance, m.eq.	−1.1	+16.3	+22.8	+34.4	+1.3	+3.7	+2.5	+16.1	+28.6	+28.2
Serum Na, m.eq./l (Value at birth 137 m.eq./l)	138	144	146	147	138	139	140	147	155	162
Serum Cl m.eq./l (Value at birth 102 m.eq./l)	103	112	116	120	104	104	101	110	117	122

modated less of the surplus water in the body than the skin, skeletal muscles and other parts of the carcass, and hence they showed a lesser degree of hydration at death. Furthermore, the concentration of Na and Cl rose progressively in the extracellular fluids in passing from experiment 1 to experiment 3 (see Table 3), and this led to progressive dehydration of the cells. In these two cellular organs this was enough to show itself as a slight reduction in the total amount of water found in the organs on passing from experiment 1 to experiment 3.

Table 3 shows the effects of adding progressive amounts of salt to the water and to the milk on the volume of urine, the visible water balance, the Na and Cl balances, and the concentration of Na and Cl in the serum. In making up these balances, and in those subsequently shown, the amounts excreted in the faeces were neglected. The figures for the three animals given water have been averaged, but owing to the complicating element of the colostrum given in experiment 2 the three milk experiments have been given separately. Sow's colostrum is a very potent food for newborn piglets, and some of its unrecognised effects will be reported later. Sufficient at

TABLE 4

The effects of adding progressive amounts of salt to the water and milk on the nitrogen and potassium balances and on the amount of nitrogen appearing as end products of protein metabolism.

(All results expressed per kg weight at birth per 24 h.)

Fluid administered ...	Water	Salted water			Milk			Salted milk			Nothing
Experiment ...	Average of 3	1	2	3	1	2	3	1	2	3	Average of 3
N intake, mg	0	0	0	0	2490	3630	2720	2570	3700	2520	0
excretion, mg . . .	183	194	106	117	236	375	323	235	356	243	122
balance, mg	−183	−194	−106	−117	+2254	+3255	+2397	+2335	+3344	+2277	−122
retained as % intake	—	—	—	—	90.5	90	88	91	90.5	91	—
appearing as end products, mg . .	213	196	123	95	202	408	305	200	382	215	142
K intake, m.eq. . . .	0	0	0	0	7.9	9.3	9.9	9.0	9.9	9.6	0
excretion, m.eq. . .	3.9	3.7	3.8	3.0	3.6	3.1	1.9	2.2	2.1	2.1	3.0
balance, m.eq. . .	−3.9	−3.7	−3.8	−3.0	+4.3	+6.2	+8.0	+6.8	+7.8	+7.5	−3.0

present to note that it greatly increases the rate of growth, and *some* of the water, minerals and nitrogen "retained" in experiment 2 were used for physiological growth over and above that possible on the later milk used for experiments 1 and 3.

The addition of salt to the water reduced the volume of the urine progressively as the concentration in the water was raised. It also increased progressively the retention of water as judged by the visible water balance, the retention of Na and of Cl as judged by their "balances", and the concentration of Na and Cl in the serum. The effects which followed the addition of salt to the milk were similar and indeed almost the same, if an allowance is made for the disturbing effects of the colostrum in experiment 2. The quantities of sodium excreted were surprisingly small considering the large amounts, over and above the needs of the animals, which were being administered. A comparison of the results for the animals given water with those for the animals given nothing, suggests a very mild degree of dehydration in the latter, but no differences in the mineral balances. In spite of the rapid flow of liquid through the tubules, therefore, the animals given water were able to retain all the Na and Cl required for the needs of their body. They did not become sodium deficient.

Table 4 shows the intake of N in the food, the amount excreted in the urine and the balances. It also shows the amounts of N which appeared as end products of protein metabolism, whether the animals were fed or

starved, and finally the potassium balances. The results confirm in all respects those given in a previous paper (McCance & Widdowson, 1956), and their bearing upon the subject of that paper requires no further comment. The results, however, confirm one feature of the previous work upon which no comment was made at that time and add new facts which will certainly require further investigation:—

(1) The piglets given water broke down considerably *more* of their tissue protein than those given nothing. This may have been the result of the movement and disturbances of the animals associated with the passage of the stomach tube for the administration of the water. This can be settled in future experiments by passing the tube without administering water.

(2) The animals given water and salt broke down *less* of their tissue proteins than those given water alone, and there is good evidence that the effect was progressive.

(3) In the animals given milk and salt *less* protein N appeared as end products of N metabolism than in those given milk alone, and again there is evidence that the effect was progressive.

(4) The animals given salted water excreted slightly less K than those given water alone, and there was certainly no increased excretion of K as has been recorded in the literature (Gamble, 1951, and see later).

The diminished excretion of K was in keeping with the diminished amounts of N appearing as end products of protein metabolism and indicates a reduced breakdown of general cellular matter. Similar results were obtained from two out of the three milk experiments in that in them the addition of salt to the milk increased the retention of K, and since it also diminished the N appearing as end products of metabolism it presumably promoted normal cellular growth. These last three effects were allied to those obtained by Leaf & Couter (1949), and by Leaf, Couter & Newburgh (1949), and the converse of those obtained in the original experiments on salt deficiency (McCance, 1936a; McCance & Widdowson, 1937). They will be discussed later.

Results on Human Infants

Clinical observations

All three babies were alert and taking food well and had no oedema when the experiments began. The first sign of change in baby 1 was a slight lethargy and then some puffiness without any true oedema. These changes were noted after about twenty-four hours on the salted milk, and soon after this the baby became less hungry, and after thirty-six hours oedema could be demonstrated and the infant became very difficult to feed and

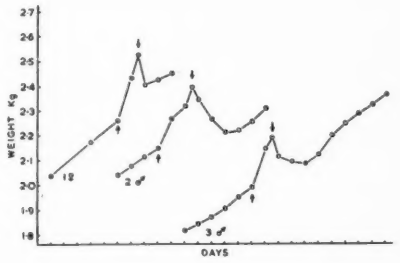

Fig. 1. The weight charts of the three infants before, during and after the period of salt administration.

lethargic till the salted milk was replaced by the normal formula. The changes in the other two infants were similar. The signs of well-being were intensified for a short time as the gain in weight began to accelerate, only to be replaced later by lethargy and puffiness till the oedema was obvious to any trained observer, and the infants became very difficult to feed. The third baby vomited about 25–30 ml after thirty hours on the experimental regime. Within twelve hours of returning to the normal diet puffiness was rapidly disappearing and the children were taking their food as well as they had been doing before the experiment began. The new-born piglets used in the present investigation were not given the opportunity of showing a loss of appetite. They did not exhibit any tendency to vomit, but in other respects the outward and visible signs of having too much salt in the food were the same in both species.

Quantitative records

Fig. 1 shows the weight charts of the three babies for some days before, and during and after the administration of the salted milk. In each case the steady gain in weight before adding the salt to the milk was greatly accelerated by its addition. The return to unsalted milk was followed by an equally rapid loss of weight until the original line of normal growth in weight had been approximately reached, when increase in weight along this line was resumed. These charts closely resemble one given by Meyer & Cohn (1911) after an experiment involving a similar change of salt intake in a full term child, as also are the clinical observations of oedema.

Table 5 gives the changes in the serum Cl which accompanied the clinical observations and the fluctuations in weight. There was an increase in the concentration in all three infants which was of the same order as that in the piglets given similar amounts of salt. The concentrations fell to normal levels during the loss of weight which took place when the administration of salt was discontinued.

Table 6 gives the periods of observation, the visible water balance and

TABLE 5

The concentration of chloride in the serum of babies before and after increasing the concentration of salt in the milk.

(m.eq./l)

Baby	Before the addition of salt	At the close of salt administration	After the resumption of the normal growth curve
1	110	120	108
2	108	119	110
3	105	119	106

TABLE 6

The water and electrolyte balances of babies before, during and after the administration of sodium chloride in the milk.

(Results expressed per kg body weight per 24 h.)

	Baby 2			Baby 3		
	Before	During	After	Before	During	After
Period of observation, min .	148	3486	885	1279	1999	2864
Water intake, ml	167	165	162	189	197	178
Urine volume, ml	174	70	149	90	70	137
Visible water balance, ml . .	−7	+95	+13	+99	+129	+41
Na intake, m.eq.	2.7	21.5	2.7	3.1	22.4	2.9
excretion, m.eq.	2.0	11.6	15.1	0.8	8.1	8.7
balance, m.eq.	+0.7	+9.9	−12.4	+2.3	+14.3	−5.8
Cl intake, m.eq.	3.1	21.9	3.1	3.5	23.0	3.3
excretion, m.eq.	3.5	11.9	13.7	1.3	8.5	10.2
balance, m.eq.	−0.4	+10.0	−10.6	+2.2	+14.5	−6.9
K intake, m.eq.	4.0	4.9	4.8	5.6	5.4	5.3
excretion, m.eq.	6.3	3.8	3.5	2.0	2.1	3.5
balance, m.eq.	−1.3	+1.1	+1.3	+3.6	+3.3	+1.8

the mineral balances, in terms of m.eq./kg/24 hr. to make them comparable with those of the piglets. These are only available for the two male infants. The body weights used in the calculations were those shown in Fig. 1, disregarding the increases due to the salt. The figures for the second baby's preliminary period were based upon too short a period of observation to make them a reliable "base line", but they are of some value and have been given.

TABLE 7

The total amounts of sodium, chloride and potassium ingested and excreted by babies during and after the time the additional salt was being administered.

	Baby 2		Baby 3	
	During	After	During	After
Na intake, m.eq. . . .	114	3.7	62	11.8
excretion, m.eq. .	61	20.6	23	35.0
balance, m.eq. . .	+53	−16.9	+39	−23.2
Cl intake, m.eq. . . .	116	4.1	64	13.4
excretion, m.eq. .	63	18.6	24	41.0
balance, m.eq. . .	+53	−14.5	+40	−27.6
K intake, m.eq. . . .	26	6.6	14.8	21.2
excretion, m.eq. .	20	4.8	5.9	13.9
balance, m.eq. . .	+6	+1.8	+8.9	+7.3

The two infants confirmed each other completely in showing: (1) A visible water balance in keeping with the changes of weight shown in Fig. 1. (2) A very large positive balance of both Na and Cl during the period in which the weights were going up unnaturally fast. The figures show that the proportions of Na and Cl retained were almost the same as those administered. (3) Large negative balances while the weights were falling. There can be no doubt to what the changes in weight were due. (4) Excretion of Na during the administration of salt greater than those of the piglets, even of those piglets to which higher concentrations of salt were given. The human infant evidently excretes Na more freely than the newborn piglet, and retains less of the amounts administered. (5) No increased excretion of K during the administration of salt. This confirmed the findings in piglets.

Table 7 gives the total amounts of the Na, Cl and K ingested and excreted during the time the additional salt was being administered, and while the weight of the two infants was falling back to the normal growth line. The observations on baby 2 were discontinued before the fall in weight was over, and this accounts for the fact that so much of the administered salt was still inside the baby at the end of the experiment. Urine was collected from baby 3 for forty-eight hours after the salt was stopped, by which time the fall in weight was completed. The amount of Na and Cl which the child still retained was just about equivalent to the amount he would have been expected to retain for true growth, as judged by the positive balances during the period before any additional salt was given.

Discussion

Recognition and nomenclature of the syndrome

The results reported in this paper have shown that the addition of too much NaCl to the food of the newborn and very young of at least two species may produce a steady state, or near steady state, in which both volume and tonicity of the extracellular fluids are considerably raised. There is no doubt that the syndrome has been met with before, and it can, in a way, be said to have been described. Schoental (1929), for example, certainly produced it experimentally in human infants, and perhaps also Stapleton in 1954. Skinner & Moll (1956) also seem to have produced it inadvertently when they were treating a baby who had been admitted after a bout of diarrhoea, and figures given by Borst (1938, 1948) show that he must have had the syndrome under observation in an adult who was undergoing treatment for a massive internal haemorrhage: "... our first patient had, thanks to the parenteral administration of much fluid, marked edema on the 4th day following operation, showing that there was surely no shortage of extracellular fluid. And yet he did not excrete any NaCl, although the NaCl concentration of the blood was excessive" (Borst, 1938). The association, however, of raised serum electrolyte concentration, which usually implies dehydration, and oedema, which indicates overhydration, has been confusing, and the syndrome has certainly not been recognised. It is suggested that it be called "hypertonic expansion of the extracellular fluids" or "hypertonic oedema". Present knowledge would indicate that the tonicity of the cells must also be raised, but this has not yet been measured. Part of the failure to recognise the syndrome as such has undoubtedly been due to the difficulty or impossibility of producing it in a normal adult and the undesirability of trying to do so experimentally in patients with nephrosis and cardiac failure, in whom it might develop quite readily.

Salt administration and protein breakdown

A relationship between the intake of salt and the breakdown of protein has been demonstrated before, but never in new-born animals and never perhaps so conclusively. McCance (1936a) showed that salt deficiency in man led to negative N balances which it was suggested (McCance, 1936b) might be attributed to defective nutrition of the cells following the reduced blood volume (see also Schoorl, 1936, and Gömöri, 1954). Leaf & Couter (1949) demonstrated the converse, also on man, and suggested that the effects were hormonal, mediated through the pituitary. In their opinion the increased intake of salt inhibited the production of both the catabolic and the salt-retaining adrenal hormones, and the effect on the former was

only temporary. This does not seem a wholly satisfactory explanation today in the light of what is now known about the regulation of aldosterone secretion (Liddle, Duncan & Bartter, 1956; Duncan, Liddle & Bartter, 1956; Bartter, Liddle, Duncan, Barber & Delea, 1956), but aldosterone may not be the only hormone involved (Blomhert, 1956). Much older work of Richards, Godden & Husband (1924), moreover, suggests that the effect may not be so shortlived as Leaf & Couter supposed, at any rate in the growing pig aged three to four months. The present experiments do not take the explanation much further, but they do show that the effect can be obtained in starving animals, and is, therefore, quite independent of the food intake. It is possible that some of the early and *apparently* beneficial results of adding small amounts of sea water to a limited ration of fresh water for dehydrated men are due to this reduction in tissue catabolism and urea production (Ladell, 1943; Whillans & Smith, 1948). It is reasonable to postulate that adding sodium chloride and some water to a limited water ration might maintain the extracellular volume for a time and thus reduce protein catabolism even if it raised the osmolar concentration of the extracellular fluids. In a healthy adult an increase in osmolar concentration of the body fluids must ultimately increase dehydration and protein breakdown (McCance & Morrison, 1956).

The excretion of potassium

A history of a relation between the administration of sodium salts and the excretion of potassium goes back to Bunge (1873). There has been a good deal of confusion, and probably more factors are involved than many have supposed. Leaf, Couter & Newburgh (1949) drew attention to the importance of the anion in normal men, and stated that whereas the administration of $NaHCO_3$ led to an increased excretion of potassium, the administration of NaCl did not. They offered a plausible explanation for this difference, and it is to be noted that Bunge (1873) had used sodium citrate, which would have given rise to the bicarbonate in the body. Gamble (1951) and his fellow workers (Gamble, Wallace, Eliel, Holliday, Cushman, Appleton, Shenberg & Piotti, 1951) gave NaCl and $NaHCO_3$, and both reduced the retention of K in a thriving infant four months old. Richards *et al.* (1924), who set out the position a good deal more clearly than many other authors either before or since, found that giving either the chloride or citrate of sodium to a young pig over a period of nineteen days increased the excretion of K in the urine, but decreased its excretion in the faeces. Leaf *et al.* (1949) cannot have been wholly right.

The relationship is evidently a real but a complicated one; yet in the present experiments there was no increased excretion of K whatsoever either

by newborn piglets or premature infants following the administration of amounts of NaCl which produced much more spectacular results than they did in any of the earlier experiments. It is submitted that the difference lay in the age of the animals used. In older animals not growing so fast the administration of sodium salts in excess of the body's requirements calls forth a series of defensive, hormonal and glandular reactions which among other things increases the excretion of K in the urine. As evidence of the complicated nature of this response, reference may be made to the work of Brunner, Kuschinsky & Peters (1956a, b). These authors found that the administration of sodium to adult rats always called forth an increased excretion of K which was not affected by vasopressin, but which was abolished by hypophysectomy and could not be restored by D.O.C.A. or cortisone. At the age studied in this investigation these mechanisms had not yet developed, or were overshadowed by the retention of K, with N, called for by the stimulus of salt.

An analysis of the cause

The immediate cause of hypertonic expansion of the extracellular fluids is clearly the establishment of the necessary conditions, and these are set out in the introductory paragraph of this paper. The same conditions cannot be maintained in adults, for adults excrete the sodium chloride in high concentrations in the urine without the same rise in the serum electrolytes, if necessary at the expense of body water. The result, therefore, of giving hypertonic sodium chloride solution to adult men or animals may temporarily be to expand the volume and tonicity of the body fluids, but these effects are quickly followed by restoration or reduction of the extracellular volume, with all the inevitable consequences which the latter entails (McCance & Young, 1944; McCance & Morrison, 1956). One of these would be an increased breakdown of tissue protein. The kidney of the infant, therefore, continues to reabsorb sodium chloride when that of an adult would certainly excrete it. This suggests a much less responsive mechanism in the newborn controlling the release or otherwise of salt-retaining hormones. Nevertheless there undoubtedly is some control, as Table 6 shows, although it may be easy to override it, and the rapid return to the healthy *status quo* as soon as the administration of salt to the infants was discontinued, shows that their volume of extracellular fluid, although relatively much larger than that of an adult, was guarded as a steady state in a very similar way. The in creased excretion of K after giving sodium to adults is not easy to explain in terms of aldosterone and fluid volumes, but since no increased excretion was obtained in these experiments there may be nothing—in newborns—to explain.

Acknowledgements

Our thanks go out to Stan and Terry Cowen for some very arduous experiments on newborn piglets, and to Miss Colbourn and Dr. Willis for their help over the premature infants. The babies were in the care of Dr. D. Gairdner, and the work on them was all done with his full co-operation.

Summary

1. Sodium chloride was added to the milk given to premature infants and newborn piglets which were then reared by hand.

2. The addition of salt led to (*a*) an abnormal increase of weight; (*b*) a rise in the serum sodium and chloride; (*c*) an expansion of the extracellular volume and ultimately massive oedema; (*d*) a reduction in the catabolism of tissue protein; (*e*) no increased excretion of potassium, if anything the reverse.

3. Similar and even more clear cut results were obtained when the piglets were given water and salted water instead of milk and salted milk.

4. When the administration of salt was stopped the infants rapidly regained their healthy status.

Expansion hypertonique des liquides extracellulaires.

Du chlorure de sodium a été ajouté au lait destiné à des enfants nés avant terme ainsi qu'à des porcelets nouveaunés qui furent alors élevés au biberon. L'addition de chlorure de sodium au lait amena: a) une augmentation anormale du poids corporel, b) une augmentation du taux du sodium et des ions chlorés dans le sérum, c) une augmentation du volume des liquides extracellulaires et subsidiairement un œdème massif, d) une réduction du catabolisme des protéines tissulaires, e) une diminution plutôt qu'une augmentation de l'élimination du potassium. Des résultats analogues et même plus nets encore ont été obtenus chez des porcelets nourris d'eau et d'eau salée au lieu de lait et de lait salé. Une fois que le sel eut été supprimé, les bébés redevinrent rapidement bien portants.

Hypertonische Ausdehnung der intracellulären Flüssigkeiten.

Kochsalz wurde zur Milch zugesetzt, die frühgeborenen Säuglingen und neugeborenen Schweinchen verabreicht wurde. Der Salzzusatz bewirkte: a. eine abnormale Gewichtszunahme, b. eine Steigerung im Natrium- und Chloridgehalt im Serum, c. eine Expansion des aussercellulären Volumens und schliesslich massives Oedem, d. eine Reduzierung im Abbau der Gewebsproteine, e. keine Erhöhung, wenn nicht Herabsetzung der Kaliumausscheidung. Ähnliche und sogar eindeutigere Resultate wurden erzielt, wenn die Schweinchen Wasser und Salzwasser anstatt der Milch und der gesalzenen Milch erhielten. Wenn die Verabreichung des Kochsalzes unterbrochen wurde, kehrten die Säuglinge rasch zu ihrem gesunden Zustand zurück.

Expansión hipertónica de los líquidos extracelulares.

Se añadió cloruro de sodio a la leche suministrada a prematuros y también a lechoncillos recién nacidos criados a mano. La adición de la sal condujo a: (a) aumentación anormal de peso, (b) ascenso del sodio y cloruro séricos, (c) expansón del volumen extracelular y finalmente edematización masiva, (d) reducción catabólica protéicoti-

sular, (e) aumento nulo de excreción potásica y más bien lo contrario. Resultados análogos y todavía màs pronunciados obtenidos cuando se suministró a los lechoncillos agua y agua salada en lugar de leche y leche salada. Al suspenderse la administración de sal, los niñitos recobraron rápidamente las condiciones de la salud.

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From the Hospital for Sick Children, Great Ormond Street, London W.C.1

The Management of Nephrogenic Diabetes Insipidus in Early Life

by EMILE GAUTIER[1] and MICHAEL SIMPKISS[2]

Nephrogenic pitressin-resistant diabetes insipidus, a rare condition occurring nearly always in boys and probably transmitted as a sex-linked recessive character (19), is a very severe metabolic disorder. In the first two years of life, all the cases reported are grossly under-weight and undersized, whilst their birth weight is normal (Fig. 1), and their psychomotor development is markedly retarded. All reported cases except one, a girl who may not belong to quite the same group as the affected boys (7), have hyperelectrolytaemia in early life.

As these children grow older, the hyperelectrolytaemia tends to subside, their general condition improves and they may compensate for their deficit in weight and height. They become more alert, but many remain mentally retarded (8, 11). It is possible that hyperelectrolytaemia contributes to the retarded mental development and the failure to thrive because hyperelectrolytaemia, with or without body water deficit, is associated with cellular dehydration and is known to cause severe neurological symptoms in human beings and experimental animals (9, 15, 20, 23). It seems, therefore, essential to make these patients normoelectrolytaemic.

In this paper, the results obtained in one case with a low solute diet will be reported as well as experiments designed to give a more precise knowledge of the circumstances in which normoelectrolytaemia and hyperelectrolytaemia occur in these children. Macdonald's studies (14) show that a close correlation exists between blood electrolyte level and urine osmolarity. Gautier & Prader suggest (10) that if enough wager could be given to excrete the renal solute load at a concentration below 75 milliosmols per litre, normoelectrolytaemia would be achieved.

Case Reports

G. D., the first child of apparently healthy parents, was born on 17.7.54, and admitted to The Hospital for Sick Children, Great Ormond Street, when 7 months old

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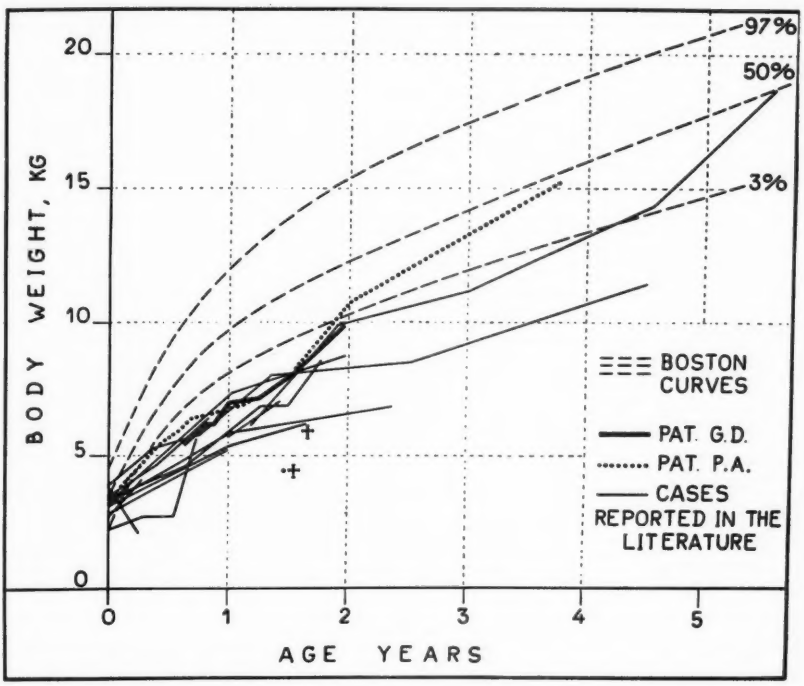

Fig. 1. Weight curves of patients with nephrogenic diabetes insipidus.

because of vomiting, constipation and a failure to thrive. Pregnancy, birth and the neonatal period were normal. He weighed 7 lb. at birth and was breast fed for 3 months. He began to vomit at one month and became worse when bottle fed at 3 months. His weight at 4 months was 11 lb. 2 oz. and in the next 5 months he gained only one pound. From the age of 4 months he had unexplained fever of up to 102°F. He was then investigated at another hospital, but despite a thorough search no cause for the fever was found. Hyperelectrolytaemia was present.

Examination.—He was moderately dehydrated and weighed 12 lb. 3 oz. There was generalised hypotonia and he was unable to sit or even support his head. He had a convergent squint, hypermetropia and made no attempt to follow a light. A smooth liver of normal consistency was felt two fingers' breadth below the costal margin in the nipple line. The genitalia were normal and the blood pressure 90/50.

During his first week in hospital vomiting and fever continued. The vomited feeds were replaced, water was offered between feeds and the fever subsided. At the same time a thirst for water was noted. The history and these symptoms pointed to a diagnosis of diabetes insipidus, the fever being due to dehydration.

Investigations.—The urine never contained protein and the sediment was always normal. The specific gravity never rose above 1.010. At the time of admission the urine output was 600 ml/24 hours, the specific gravity 1.008 and the pH 6.3. On

4.3.55, the plasma sodium was 176 m.eq/l and plasma potassium 4.9 m.eq./l, plasma chloride 123 m.eq./l and plasma bicarbonate 35.6 m.eq./l.

Pitressin tests were done using water soluble pitressin intramuscularly (Parke Davis). The batch used was active. In order to have an unvarying flow during the test the water load was kept constant by dividing the daily water intake by 12 and giving this amount hourly. Normal children respond to 0.5 units of Pitressin per square metre of body surface area by a reduction in urine volume and a corresponding rise in solute concentration and specific gravity (11). At 9 months, a pitressin test was done using this dosage (0.15 units being given). The test was repeated using five times the dose (0.75 units being given), this produced the side effects of blanching and sweating. At 13 months the test was repeated using the standard dose (0.2 units were given). On none of these occasions did pitressin have any effect on urine flow or concentration, so that the diagnosis of pitressin resistant nephrogenic diabetes insipidus was made.

A combined inulin and urea clearance was done when he was 20 months old and fully hydrated. The blood urea was 36 mg %. During the first and second half hour periods respectively inulin was cleared at 83 and 97 ml/min/1.73 m². The urea/inulin ratios were 0.58 and 0.55 respectively. These clearances are below normal for his age (16).

Progress (Fig. 2).—When first in hospital he was given 35 oz. of full cream National dried milk a day, and 30 oz. of water were given between feeds in divided amounts. He gained weight slowly and marked hyperelectrolytaemia persisted. An attempt was made to cut down his urinary solutes by giving a dried milk with a low sodium content (Edosol). Although there was some improvement in the hyperelectrolytaemia he gained weight very slowly and the urinary solute output was reduced further by giving very small amounts of Edosol and ensuring an adequate caloric intake by adding double cream and glucose. This diet was very low in protein and sodium. Whereas previously he had 22 g of protein daily, he was now getting 3 g only. At times normoelectrolytaemia was achieved and he gained weight much more rapidly. At the same time his ability to drink water increased. The very low protein diet was given for 4 months. During the fourth month he lost weight. This was probably due to breakdown of tissue protein. The protein and fluid intakes were then increased step by step. When he was 14 months old he was drinking 100 ounces daily and became normoelectrolytaemic. At 16½ months there was an episode of unexplained vomiting. He was given half strength Hartmann's solution which was an error, and loss of weight and hyperelectrolytaemia occurred. When 18 months old, although he would not eat solids, he was having a normally balanced diet.

Despite the long period of low protein intake there was neither clinical nor laboratory evidence of liver damage. Serum paper electrophoresis and liver function tests before and after this period were both normal.

Mental progress has been striking. Within three weeks of starting the low solute diet he was looking about, playing and could lift his head. He even tried to sit up. From then on progress was steady and now at 2 years his mental age is about the 18 month level. He weighs 22½ lbs. and is 30″ long. Although he is still below Boston 3rd percentile, he has made up part of his weight deficit.

P. A. was born on 14.6.52, and was admitted at the age of 9 months with a history of occasional vomiting from the fourth month and failure to thrive since the sixth month. A diagnosis of pitressin resistant diabetes insipidus was made. He has been fully

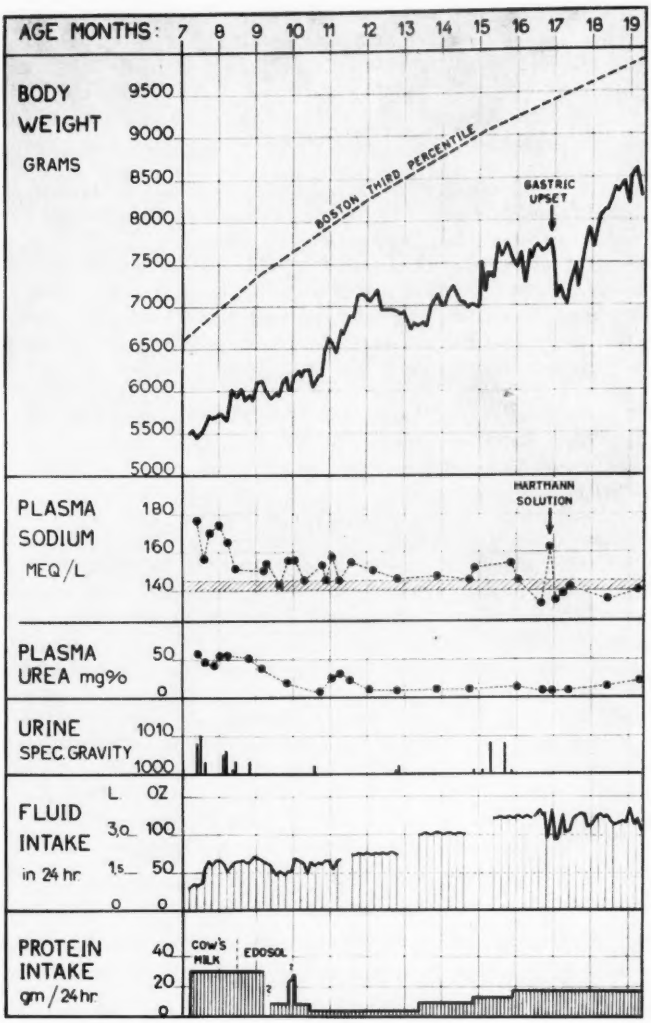

Fig. 2. Progress of patient G. D.

reported by Luder and Burnett (13). At no time were albumin or casts present in the urine. Urea clearance was normal on two occasions (maximal clearance 68 % and 76 %), and a little low on a third occasion (maximal clearance 54 %). The blood urea which was raised became normal when the child was fully hydrated. He made poor progress when in hospital. When 18 months old he was able to hold a cup and drink

from it and from that time on he has gained weight steadily. At 3 years 9 months he weighed 35 lbs. (Boston 50th percentile) and was 35 ⅜″ high (Boston 3rd percentile). There is slight mental retardation.

Methods

In patient P. A., at the age of 3 ½ years, six-hourly urine collections over a thirty hour period and one specimen of blood were obtained at home before, and several days after changing from a low solute to a normal diet.

In patient G. D., at the age of 20 months, similar urine collections were made with serial measurements of body-weight and blood chemistry. In other experiments, the water intake and/or the solute load were varied over approximately 10-hour periods. An increased solute load was produced by giving large amounts of salt-free milk (Edosol) in order to increase the urea excretion without increasing the salt intake. This was done in order to avoid the effects caused by the strong tendency of these children to retain sodium chloride (10). A metabolic chair was used and fluids were given by mouth. Urine was passed spontaneously and weight recorded immediately after micturition. The child was offered water to drink ad lib. for 2–3 hours before the experiments started.

Total osmolarity was measured either by the freezing point depression method, using a Beckmann type thermometer or by measurement of the depression of vapour pressure. For this a Baldes-Hill type of thermoelectric osmometer (1) was built by one of us (E. G.). Throughout the text, one milliosmol corresponds to a depression of the freezing point or of the vapour pressure equivalent to that produced by one milliosmol of sodium chloride.

Sodium chloride, potassium and urea were determined by the routine methods used in this hospital (22).

Vesterdal's technique was used for inulin clearance (18). The inulin was measured using a micromodification of the method of Barnett et al (2). Van Slyke's method was used for urea clearance.

Results

Patient G. D.

During these experiments, G. D. was always eager to drink tap water or 5 to 10% glucose in water. He drank full-strength Edosol willingly, but drank double-strength Edosol reluctantly. After a while he refused it though at that time he would drink water or glucose in water with great eagerness. When offered double-strength Edosol, he showed his thirst by making suction movements with his lips but as soon as he realized what he was being offered he turned away his head and thrust away the cup. On one occasion he vomited and immediately looked more cheerful. The double-strength Edosol had then to be diluted in order to continue the experiment.

The following results were obtained:

Experiment 1: Intake of tap water varied whilst fasting

When water was given at a rate of 50–100 ml per hour, the weight decreased. When the intake was increased to 150 ml per hour, the weight became stable. With a water intake of 180–240 ml per hour he gained weight, the urine osmolarity decreased from 80 to 56 milliosmols per litre; the rate of solute output was fairly constant around 10 milliosmols per hour and the blood chemistry was normal throughout.

Experiment 2: Loading with full-strength Edosol (Fig. 3)

When full-strength Edosol was given at a constant high rate (200 ml per hour) over a period of eight hours, there was an initial gain in weight, after which the weight fluctuated although there was no true fall. The sharp increase in solute excretion two hours after the beginning of the experiment suggests that the initial weight gain was due to accumulation of the milk mixture in the gastro-intestinal tract before it was absorbed. The urine osmolarity fluctuated between 70 and 90 milliosmols per litre, urea making up 30 milliosmols per litre. The rate of solute output was markedly but irregularly elevated. The urinary potassium/sodium ratio remained constant. The blood urea increased from 29 to 44 mg%. The blood electrolytes were unfortunately not determined.

Experiment 3: Loading with double strength Edosol (Fig. 4)

The same amount of dry Edosol powder was given in half as much water at a rate of 100 ml per hour. The weight after an initial increase, fell steadily. The urine osmolarity rose from 60 to 160 milliosmols per litre, urea making up for 93 milliosmols per litre in the last urine specimen. The rate of solute excretion was similar to that produced by full-strength Edosol. The urinary potassium/sodium ratio rose markedly, as the rate of potassium excretion, but not that of sodium excretion increased. The blood urea rose from 36 to 64 mg% plasma sodium from 152 to 157 m.eq./l, plasma chloride from 117 to 119 m.eq./l. Because the child was insufficiently hydrated at the beginning of this experiment (raised sodium and urea) it was repeated. A loss of weight of 225 grams occurred. The urine osmolarity rose from 50 to 170 milliosmols per litre. The urinary potassium/sodium ratio increased markedly. The plasma sodium concentration rose from 147 to 158 m.eq./l, chloride from 117 to 121 m.eq./l, and urea from 17 to 26 mg%, but the weight loss between the two measurements of the plasma electrolytes was 80 grams only.

Experiment 4: Reduction in solute output

After 7–10% glucose in water had been given for 48 hours, 10% glucose in water was given at a rate of 100 ml per hour. There was an initial weight

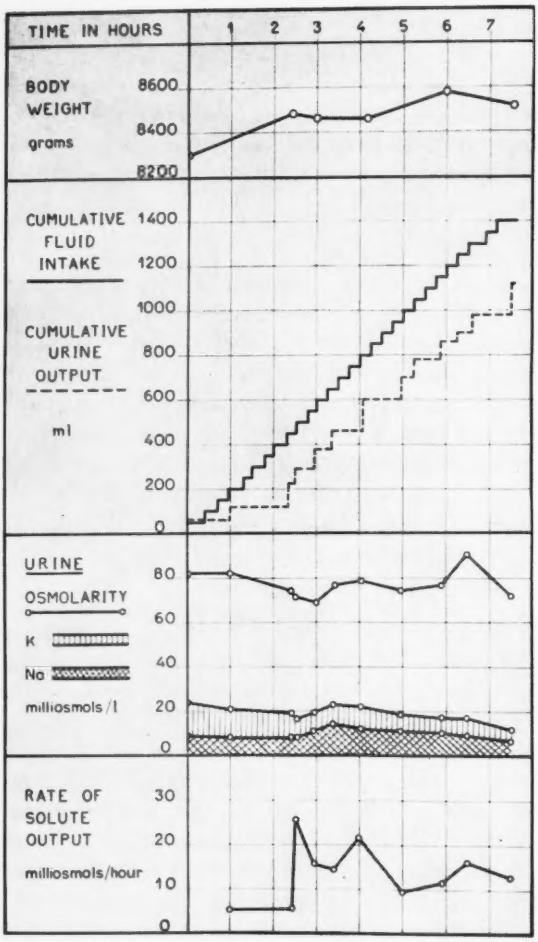

Fig. 3. Experiment 2. Full-strength Edosol by mouth. Pat. G. D.

gain and after that a steady, very slight fall with an overall loss of weight of only 30 grams. The urine osmolarity was between 20 to 45 milliosmols per litre and the rate of solute output was very low (3–5 milliosmols/hour). Plasma urea was only 6 mg%. There was an unexpected rise in the plasma electrolytes at the end of the experiment which may be a technical error as the specimen was kept for three days before being analysed.

Experiment 5: Water deprivation

Body weight, plasma electrolytes and urine osmolarity were followed during 24 hours. The child was offered water ad lib., except between mid-

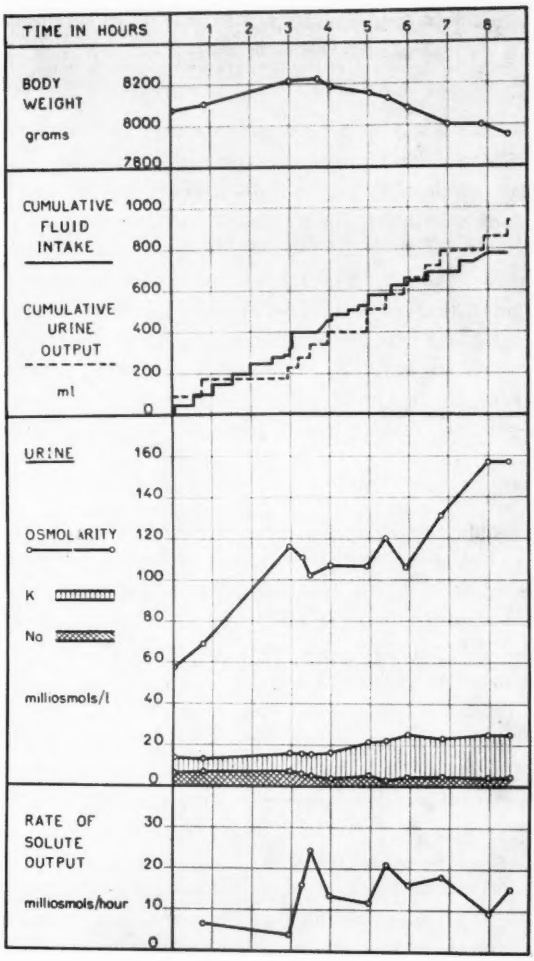

Fig. 4. Experiment 3. Double-strength Edosol by mouth. Pat. G. D.

night and 6 a.m., when he received none. The diet contained a moderate amount of cow's milk, and the urine solute output was 140 milliosmols during these 24 hours. By day, the water intake exceeded the urine output, the child gained weight and the blood chemistry was normal (plasma sodium 144 and 145 m.eq./l). The urine osmolarity was around 40 mos/l. During the six hours of water deprivation he lost 650 g in weight, there was definite hyperelectrolytaemia at the end of this period (plasma sodium 163 m.eq./l, chloride 122 m.eq./l), the potassium/sodium ratio and rate of

potassium excretion increased markedly but the urine osmolarity rose only to 50 milliosmols per litre.

Patient P. A.

On regime A, he was given a diet containing a small amount of sodium free milk and mostly carbohydrate and fat. The total solute output was 209 milliosmols per 24 hours. With regime B, a normal diet for him, containing ordinary milk, the 24-hour solute output was 353 milliosmols per 24 hours. In both experiments, the child drank water ad lib. The urine volume was 3128 ml on regime A, 3360 ml on regime B. The range of solute concentration was 51–90 milliosmols per litre on regime A, 98–116 milliosmols per litre on regime B. The urine osmolarity at 9.0 a.m. after he had drunk water ad lib. for two hours was 53 mosmols/l on regime A, and 100 mosmols/l on regime B. The plasma sodium was measured at the same time, and was 144 m.eq./l with regime A but was raised to 154 m.eq./l on regime B.

Discussion

These experiments are open to many criticisms. The retention of milk in the stomach before it was absorbed caused discrepancies between the external weight changes and changes occurring actually inside the body. Incomplete bladder emptying also causes inaccurate timing of the urine collections. Our aim was, however, to reproduce natural conditions as closely as possible.

These experiments were done to find under what circumstances normoelectrolytaemia can be maintained, in an effort to make practical rules which one could apply in the dietary treatment of these children.

Water deprivation leads in a few hours to severe dehydration with only a very slight increase in urine osmolarity.

An increase in the renal solute output leads to loss of weight and hyperelectrolytaemia if the water intake is not sufficiently increased at the same time. In these circumstances, water is lost in excess of body electrolytes, and not in proportion to the body solutes which are carried through with the loading solute, as seen during the so-called osmotic diuresis in a normal subject. The fact that the rate of excretion of sodium did not rise at all was very striking. The rate of excretion of potassium did rise, so that some intracellular water has probably been made available to cover the renal losses. The urine osmolarity increased much more than during water deprivation, but the highest value obtained was only 170 milliosmols/l.

When plasma sodium is plotted against body weight (Fig. 5) at the time the blood specimen was obtained, a fair negative correlation can be seen. If we assume that during the six weeks that these experiments lasted the

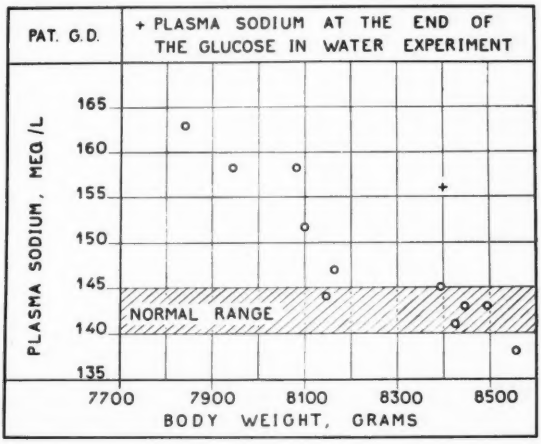

Fig. 5. Relationship between plasma sodium level and body weight. Pat. G. D.

fat and the solid content of patient G. D. did not vary, this indicates that the level of sodium is inversely related to the degree of hydration of the body. Hyperelectrolytaemia appears when the child becomes dehydrated. Except for the unexpected result at the end of the glucose in water experiment, normoelectrolytaemia seemed to be present more regularly when the body weight was above 8.3 kg.

When plasma sodium is plotted against urine osmolarity (Fig. 6) there is not the close correlation that was observed in Macdonald's case where

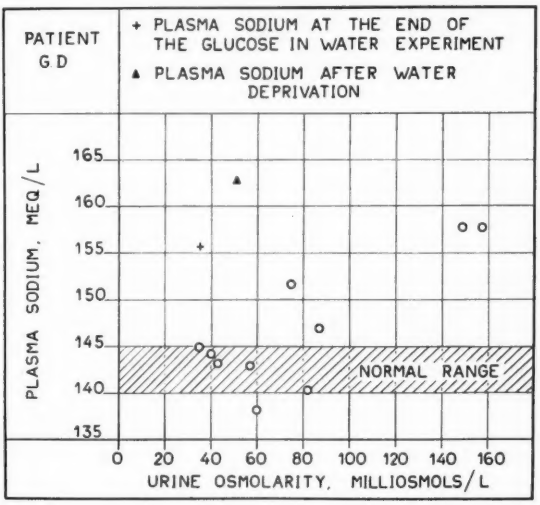

Fig. 6. Relationship between plasma sodium level and urine osmolarity. Pat. G. D.

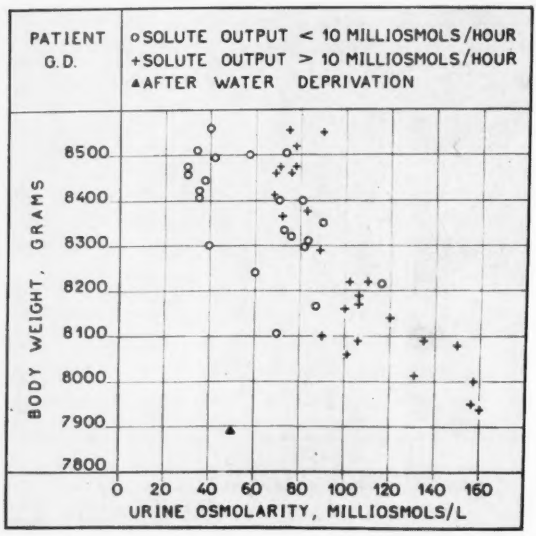

Fig. 7. Relationship between urine osmolarity and body weight, and influence of solute output. Pat. G. D.

the experimental conditions were less variable, because they did not include changes in the renal solute output or a period of water deprivation. Hyperelectrolytaemia occurs at any level of urine osmolarity. But it seems that normoelectrolytaemia can be obtained only, if not always at a urine osmolarity below 90 milliosmols/l.

The inverse relation between urine osmolarity and body weight is shown in Fig. 7. The value obtained at the end of the period of water deprivation does not, however, agree with the general pattern. The points corresponding to the low rate of solute output tend to stand to the left of the group. Urine osmolarities up to 90 milliosmols/l were observed with a body weight above 8.3 kg.

The variations in weight during the periods corresponding to the urine specimens were studied. In Fig. 8 each point represents a specimen of urine. Solute concentration is plotted against the rate of urine solute output. The variation in weight during the period corresponding to the urine specimen is indicated. Weight loss can occur at any level of urine osmolarity or solute output. That weight loss can occur with a very low urine osmolarity means that there is probably little danger of water intoxication. Weight gain on the other hand occurs mainly if both the rate of solute output and the urine osmolarity are low.

When the patient G. D. was having his normal diet and the water was

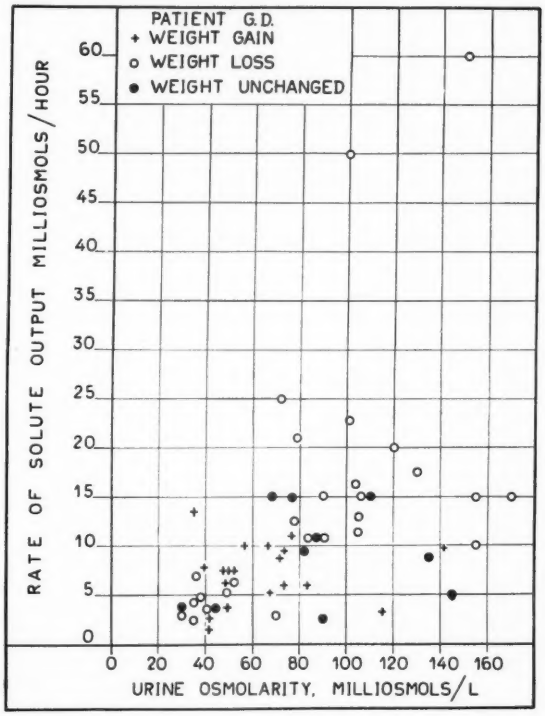

Fig. 8. The influence on weight of the relationship between solute output and urine osmolarity. Pat. G. D.

offered ad lib., his urine osmolarity was around 40 milliosmols/l, and the plasma sodium was normal, except after six hours of water deprivation.

Patient P. A. was normoelectrolytaemic when able to excrete the renal solute load at urine concentrations varying from 51 to 90 milliosmols/l. His plasma sodium was raised when on regime B the urine osmolarity ranged from 98 to 116 milliosmols/l. It is also to be noted that when Gautier and Prader's patient had a urine osmolarity varying between 114 and 145 milliosmols/l, his plasma sodium was raised. Macdonald's patient became normoelectrolytaemic only when the urine specific gravity was 1001 or less.

To summarize, it seems that a child with nephrogenic diabetes insipidus will be normoelectrolytaemic if enough water is given for the renal solute load to be excreted at a concentration below 90 milliosmols/l. If the rate of solute output is low, it may be necessary to maintain a urine concentration as low as 50 milliosmols/l.

A study of the literature shows that this critical range of urine osmolarity compatible with normoelectrolytaemia is probably related to some funda-

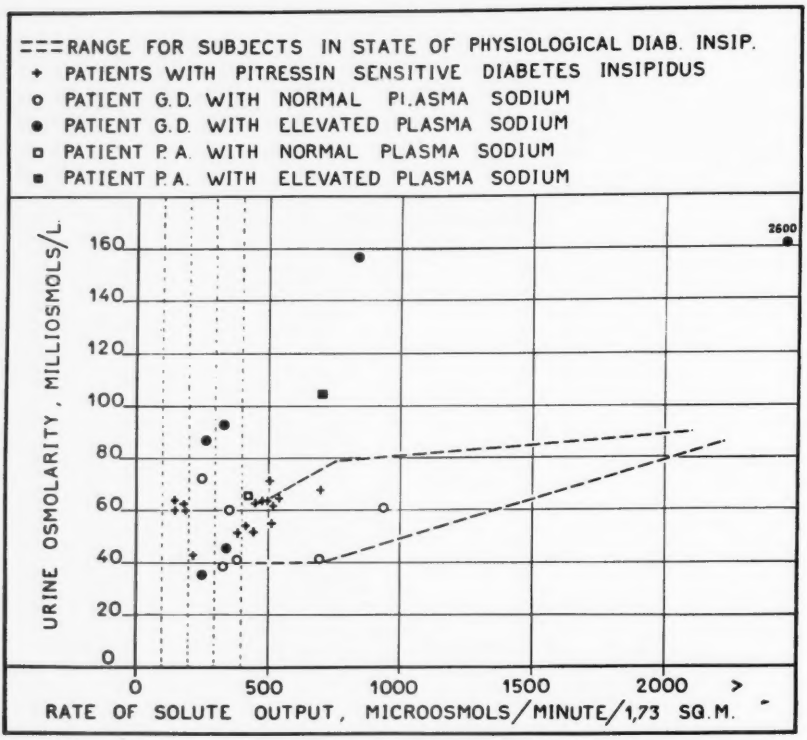

Fig. 9. Relationship between urine osmolarity and solute output in physiological diabetes insipidus, in pitressin-sensitive diabetes insipidus and in nephrogenic diabetes insipidus.

mental law of the function of the kidney when antidiuretic hormone is not acting.

In normal subjects in a state of functional diabetes insipidus (where the endogenous production of A.D.H. is inhibited by a state of overhydration) (12), and in patients with pitressin sensitive diabetes insipidus receiving no pitressin and drinking water ad lib., a direct relationship between urine flow and rate of solute output is observed (3, 17).

The relationship is the same for both groups. Accordingly, there is a slight direct relationship between urine osmolarity and rate of solute output (Fig. 9). At low rates of solute output, the urine osmolarity varies from 40 to 70 milliosmols/l. For a high rate of solute output, the urine osmolarity rises up to 80 milliosmols/l. The rise in urine osmolarity as the rate of solute output increases never reaches the plasma osmolarity: it is assumed that this rise is due to the addition of more and more proximal, isotonic, urine

to a more or less fixed quantity of water secreted, or not reabsorbed, in the distal tubule (5, 21).

The results obtained in our two patients are shown in Fig. 9. The indicated points represent mean values of urine specimens collected over the two hour periods during which the plasma chemistry was estimated. As long as the plasma sodium is normal, the results fall in the same range as the subjects with physiological diabetes insipidus or the patients with pitressin sensitive diabetes insipidus receiving no pitressin and drinking ad lib. When the plasma sodium is raised, the results are well above this range. However, the urine specimens obtained after water deprivation and at the end of the glucose in water experiment fall inside the "normal" range, despite an elevated plasma sodium.

By giving a hypertonic solution of mannitol intravenously, Brodsky and Rapoport (5) have produced a rapid weight loss and a rise in plasma osmolarity in patients with pitressin sensitive diabetes insipidus receiving no pitressin, and who were not allowed to drink.

The values for urine osmolarity and rate of solute output of the urine specimens obtained under these circumstances would fall well above the "normal range" if plotted on Fig. 9.

We can therefore make a practical rule for the treatment of nephrogenic diabetes insipidus. In order to avoid hyperelectrolytaemia, enough water must be given to maintain the relationship between urine osmolarity and rate of solute output which is observed when no antidiuretic hormone is acting.

The total solute output per day has been measured in 24 children receiving a normal diet, ranging in age from 1 month to 7 years. There was a large scatter, but on an average the solute output was 25 milliosmols/kg/day or 550 milliosmols/sq. m/day. We did not observe a reduction in the rate of solute output per unit of weight or surface area with an increase in age. Our patients, whilst on a low solute diet, excreted from 14 to 16 milliosmols/kg/day or from 340 to 350 milliosmols/sq.m/day.

For rates of solute output between 350 and 550 milliosmols/sq.m/day (420 to 660 microosmols/min/1.73 sq.m) the normal range of urine osmolarity when A.D.H. is not acting is between 40 to 70 milliosmols/l. Making the calculation with a urine osmolarity of 55 milliosmols/l, a normal diet would require a urine volume of 450 ml/kg/day, or 10 litres/sq.m/day. A low solute diet would require a urine volume of 300 ml/kg/day or 6.4 litres/sq.m/24 hours. A very large water intake results, which must cover, of course, the extra-renal water requirement as well (500 ml/sq.m/24 hours if there is no fever etc.).

Although we did not use breast milk as a source of protein instead of salt poor, dried milk it should be tried in the first two years of life, for

several reasons: Symptoms often started after weaning. Breast milk has a lower electrolyte content and contains a protein of higher biological value than cow's milk, hence there must be a decreased solute load. As the stomach empties more quickly, the child is willing to drink more.

It is in infancy that the two complementary therapeutic measures, an increase in water intake, and decrease in solute output, are the most difficult to realise.

There are several reasons why the water intake cannot be sufficiently increased: There may be a temporary real lack of thirst, with no eagerness even for water, seemingly related to the mental apathy produced by severe, prolonged dehydration (10, 14). There is an apparent lack of thirst, which is probably a protective refusal of too concentrated milk foods. The child tends to vomit. The stomach capacity is limited. The child has no voluntary access to water.

The urinary solute output cannot be decreased sufficiently: Reduction in the salt intake will not alone reduce the solute load enough. The minimum to which the protein intake can be reduced is not as low as later in childhood, because the metabolic rate, the turnover of protein, and the requirements for growth are higher. Dehydration fever also increases the metabolic rate.

As the child grows older, he gets voluntary access to water, his thirst is by then usually very marked, his stomach capacity has increased proportionally much more than his metabolic rate, his nitrogen turnover and his protein requirements (4). The fever disappears with better hydration. These facts probably explain why a very definite improvement is encountered around the end of the second year of life.

The difficulties met with during the treatment are very well demonstrated in our case: Fig. 2. When the protein intake was normal, and as much, but not enough, water as possible was given there was hyperelectrolytaemia and poor weight gain. Replacing cow's milk by salt free milk did not lower the solute output sufficiently to produce normoelectrolytaemia. A drastic diminution of the protein intake allowed a better hydration, but was soon followed by weight loss, probably due to the insufficient protein intake. It was then possible to increase step by step protein and water intake while still maintaining normoelectrolytaemia. At the same time, the child was able to make up for part of his weight deficit.

Conclusions

The requirements for normoelectrolytaemia in nephrogenic diabetes insipidus have been defined. It seems that in early life, the requirements for normal metabolism and growth and normoelectrolytaemia are practically incompatible.

If we believe that hyperelectrolytaemia is an important factor in causing mental retardation we shall be justified in giving a low protein diet even if growth is retarded. This should be continued only as long as the child does not drink sufficient water to maintain normoelectrolytaemia when taking an adequate normal diet. It is equally important to give water to the baby throughout the 24 hours. The recognition of female carriers (6) will make an early diagnosis and treatment possible.

Acknowledgements

We should like to thank Dr. Bernard Schlesinger and Dr. Wilfred Sheldon for permission to study their cases; Dr. W. W. Payne for his advice and encouragement, and Dr. R. Lightwood for kindly allowing us to use the freezing-point osmometer in the Paediatric Unit at St. Mary's Hospital. None of this work would have been possible without the help of the nursing staff to whom our thanks are also due.

One of us (E. G) would like to thank the Research Committee of The Hospital for Sick Children, Great Ormond Street, for their support.

Summary

In two patients with nephrogenic diabetes insipidus, the requirements for normoelectrolytaemia have been defined in terms of water intake and solute output. The principles and difficulties of treatment are discussed.

Traitement du diabète insipide rénal chez les tout jeunes.

Pour deux malades atteints de diabète insipide rénal, la normoélectrolytémie se base sur le contrôle de la ration hydrique et de l'excrétion des solutés. Les principes et les difficultés du traitement sont discutés.

Die Behandlung des nephrogenen Diabetes insipidus im frühen Alter.

Bei zwei Kranken mit nephrogenem Diabetes insipidus wurden die Erfordernisse für Normoelektrolytämie, ausgedrückt in der Quantität der Wasseraufnahme und der ausgeschiedenen Lösungen, bestimmt. Die Grundsätze und Schwierigkeiten der Behandlung werden erörtert.

Tratamiento de la diabetes insípida nefrogena en la edad temprana.

Defínense los requisitos normoelectrolitémicos de dos pacientes afectos de diabetes insípida nefrógena, bajo los conceptos de ingreso acuoso y rendimiento soluto. Discusión de los principios y dificultades del tratamiento.

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Hiatus Hernia in Children

by H. ENGBERG, G. THOMSEN and J. VESTERDAL

Some thirty years ago Åkerlund published his important paper on hiatus hernia. Among the 23 patients mentioned in the article there was one child. This child had been examined at the Rigshospital in Copenhagen and the case history was included in Åkerlund's series by the courtesy of H. J. Panner, lecturer in radiology. This patient has been re-examined by us and his history runs as follows:

The patient was born in 1917. From early childhood vomiting was a prevalent symptom and haematemesis occurred at frequent intervals. Fluids were well tolerated and his food was prepared accordingly. As a child he always kept a bowl at his side in case vomiting should start unexpectedly. Gradually he made it a habit to masticate his food thoroughly and so vomiting subsided. Haematemesis did not occur in adult life. He was several times admitted to hospital for dietary treatment which, however, was without benefit. Operation and bouginage were not considered. He now eats almost everything and lives an active and responsible life. He participates in dinner parties under the mutual understanding with the hosts that he has to be placed at the table where he has easy access to the door, so he can leave the table if necessary. If this has not been arranged he gets nervous, and food which he would otherwise be able to swallow sticks in the oesophagus. Radiological examination (1955): No dilatation of the oesophagus. A short constriction is seen above a sliding hiatus hernia about the size of a fist. The folds of the gastric mucosa are seen passing into the hernia through a large opening. Regurgitation is present in Trendelenburg's position and on leaning forward. His physical appearance is normal.

The incidence of hiatus hernia in children is not known. Doubtful cases may be incorrectly diagnosed as rumination or pyloric stenosis. Carré *et al.* (1953) have published 112 cases from Birmingham. They are of the opinion that in a paediatric department the ratio of pyloric stenosis/hiatus hernia is 5/1. Due to the fact that a number of cases of hiatus hernia are cured spontaneously in the first two years of life only a few cases are diagnosed after the second year. Only children with severe symptoms will present themselves for radiological examination, and a thorough radiological examination is by no means easy in an obstinate child.

Radiological examination reveals regurgitation, disappearance of the gastro-oesophageal angle and protrusion of a small part of the stomach through the hiatus into the thoracic cavity. The gastric rugae are often clearly visibly here. In some cases the cardia is wide but more frequently it appears as a constriction a short distance above the diaphragm. On fluoroscopy one can see the contrast medium move through an incompetent cardia synchronously with the respiration or when the child cries. In order to investigate whether this finding occurs in normal children one of the authors (G. T.) has examined 145 normal children in the age group 0–6 years. No cases of regurgitation were found.

The main symptom is vomiting. Generally the child starts vomiting just after birth or in the first weeks of life. The ejected material consists of ingested food mixed with mucus, sometimes with a little blood. Melaena or a large haematemesis is rare except in cases of obvious oesophageal ulcer. Gastric peristalsis may be visible. Common findings are anaemia, failure to thrive or weight loss. In the later part of infancy the vomiting is less pronounced and may occur only when the child is lying in the recumbent position or when coughing.

In early life it may be difficult to tell the difference between pyloric stenosis and hiatus hernia because the symptoms of visible gastric peristalsis and profuse vomiting may also be present in the latter condition. At a later date other diseases may have to be considered, such as duodenal ulcer, malrotation of the intestine, intestinal obstruction or kidney diseases accompanied by acidosis. Coughing caused by overflow of regurgitated material into the larynx may simulate bronchitis or other respiratory diseases.

Since 1926 numerous papers concerning the incidence, symptoms and therapy of hiatus hernia have appeared. These papers have been extensively reviewed in a monograph by one of the authors (Thomsen, 1955). Most of the literature is concerned with hiatus hernia in adults. These hernias in adults are acquired and generally first give symptoms at the age of 40–60 years. Recent reports have shown that hiatus hernia occurs not infrequently among children especially in infancy. The aetiology and symptoms of hiatus hernia in infants are somewhat different from those found in adults.

In previous papers the hiatal hernias have been classified in various ways. In this paper the following classification is used: (1) *Para-oesophageal hernias* in which the cardia is in its normal place but the fundus of the stomach has herniated into the thoracic cavity lateral to the oesophagus (see Fig. 1). (2) *Sliding hernias*. The cardia is situated above the diaphragm and the contents of thehernia consist of the abdominal part of the oesophagus and the adjoining part of the stomach. The sliding hernias can be subdivided

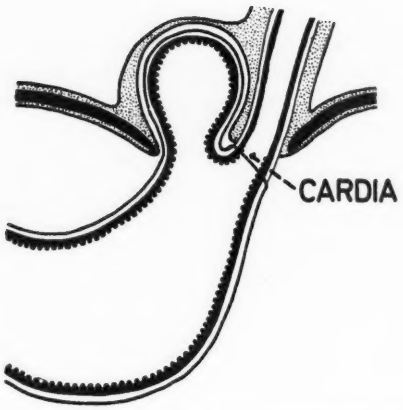

Fig. 1 (*left*). Para-oesophageal hiatus hernia.

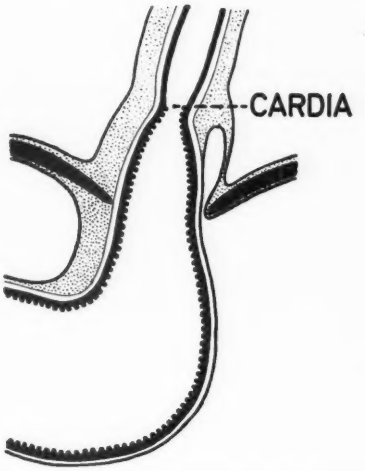

Fig. 2 (*right*). Sliding hiatus hernia without oesophageal pathology.

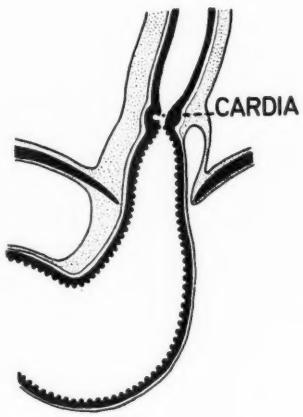

Fig. 3 (*left*). Sliding hernia with oesophageal ulcer.

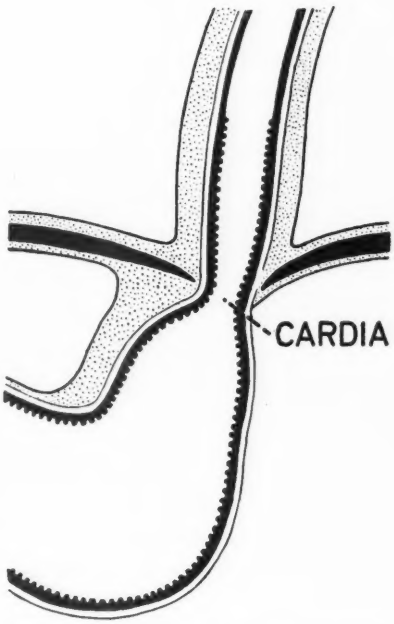

Fig. 4 (*right*). Congenital short oesophagus.

into 2 groups, (*a*) without oesophageal pathology (Fig. 2.) and (*b*)) with eosophageal pathology (Fig. 3.). (3) *Barrett's congenital short oesophagus* (Fig. 4) (see below).

In the para-oesophageal hernia the sphincter mechanism at the cardia is competent. In the sliding hernias the cardia is always incompetent, allowing the contents of the stomach to regurgitate into the oesophagus under favourable conditions, i.e. when the patient is in the Trendelenburg or horizontal position or is leaning forward. The regurgitation may damage the mucous membrane of the oesophagus and not infrequently cause secondary changes in the wall of the lower part of the oesophagus giving rise to spasm, stricture, fibrosis or peptic ulcer. When the hernia is constantly present, the oesophagus will generally appear too short on the radiological picture. This condition has been termed brachyoesophagus (thoracic stomach) and congenital short oesophagus. In almost all cases this shortening is secondary, caused by damage to the wall of the oesophagus by the gastric juice.

In 1950 Barrett used the term "congenital short oesophagus" to describe a condition in which the part of the oesophagus lying above the diaphragm is coated with a layer of gastric mucosa.

Many theories have been put forward concerning the cause of the incompetence of the sphincter in sliding hernias. The most important factor in producing an efficient sphincter action is presumably the oblique entering of the oesophagus into the stomach. Of secondary importance are the oblique muscle fibers in the stomach wall and the muscles of the diaphragm surrounding the oesophagus. Apparently there is no definite sphincter at the cardia, at least not in the accepted anatomical sense.

Present Series

The series comprises 63 cases. The disease was diagnosed radiologically before the age of 10 years in 60 cases. Three patients had characteristic symptoms from birth but the radiological diagnosis was not made until after the age of 10 years. Five patients had paraoesophageal hiatal hernias and 58 sliding hernias. In addition to the sliding hernia 27 patients presented radiological signs of spasm in 7 cases, fibrosis in 7 cases and peptic ulcer of the oesophagus in 13 cases. At operation 3 of these were classified as "congenital short oesophagus".

Most of the cases have been diagnosed during the last 7 years and all have been re-examined clinically as well as radiologically. Dividing the patients into surgically treated and medically treated cases two almost equal groups were found (Table 1).

TABLE 1

63 children suffering from hiatus hernia. Classification according to treatment and type of hernia.

Type of hernia	Medical treatment	Surgical treatment	Total
Para-oesophageal hernia . .	0	5	5
Primary sliding hernia without evidence of oesophageal pathology	17	15	32
Sliding hernia with evidence of oesophageal pathology	12	11	23
Congenital short oesophagus	0	3	3
Total	29	34	63

In recent years the conservative treatment has consisted of prevention of regurgitation by placing the infant in the sitting position during and after feeding and during sleep. In a few cases the symptoms have been so slight that no treatment was necessary. In the cases with symptoms arising from stenosis the treatment has mainly been directed towards the relief of this. The results of the treatment have been evaluated at a follow-up examination. The average observation time was 5 years and the shortest observation time 2 years. The criteria of complete recovery have been: (1) no radiologically demonstrable hiatus hernia or regurgitation, and (2) no clinical symptoms.

The results of the follow-up examination appear in Table 2. In 3 of the 4 patients who died the cause of death had no relation to the hiatus hernia which was still giving symptoms at the time of death (one died from nephro-

TABLE 2

Results of medical treatment of 29 children suffering from hiatus hernia.

Sliding hernias	Cure	No cure	Deaths	Total
Without signs of oesophageal pathology (spasm, stenosis, oesophagitis)	10	5	2	17
With signs of oesophageal pathology	1	9	2	12
Total	11	14	4	29

TABLE 3

45 operations for hiatus hernia in 34 children. Age at operation and classification according to type of hernia.

	Para-oesophageal hernias	Sliding hernias		Congenital short oesophagus	Total
		− oesophageal pathology	+ oesophageal pathology		
Age at operation (years)					
0 − 1	0	9	4	0	13
2 − 3	2	9	4	2	17
4 − 6	1	1	4	1	7
12 − 22	3	0	3	2	8
No. of operations	6	19	15	5	45
No. of patients	5	14	12	3	34

lithiasis and uraemia, one from plasma cell pneumonia and one from enteritis. In the last case pronounced symptoms of stenosis were present and a jejunostomy was performed. The patient died 9 days after the operation). The number of surgically treated patients was 34. Some of these were operated upon twice because of recurrence of the hernia so that a total of 45 operations were performed. The age distribution at the time of operation can be seen in Table 3.

A left thoracotomy was performed and aimed at a reduction of the hernia. In the 27 herniotomies performed before 1951 fixation of the cardia to the oesphageal hiatus was carried out with silk sutures. The frequent recurrences, however, made an improved technique desirable and in the 12 herniotomies performed after 1951 a new procedure was adopted. After reduction of the hernia the cardiac notch was reconstructed by sutures uniting the oesophagus to the fundus of the stomach and in addition the fundus was sutured to the lower surface of the diaphragm which was deprived of its peritoneal covering. In 2 cases of para-oesophageal hiatus hernia the operation was performed through an abdominal incision. In 3 very young infants the only operation performed was a left phrenicotomy. It was suggested that a temporary elevation of the left dome of the diaphragm would carry the fundus upwards making the cardiac incisura more pronounced and facilitating a reduction of the hiatus hernia. Gastro-oesophageal resection was performed in 3 cases of congenital short oesophagus.

TABLE 4

34 children suffering from hiatus hernia undergoing operations.

	Cure	No cure	Total
Para-oesophageal hernias	3	2	5
Slidings hernias without oesophageal pathology	10	4	14
Sliding hernias with oesophageal pathology	3	9	12
Congenital short oesophagus	3	0	3
Total	19	15	34

15 children of the 34 operated upon were not cured. 8 of the 15 presented a hernia or a stenosis at the follow-up examination but were almost free of symptoms. 7 of the 15 had a hernia or stenosis and still presented symptoms of the disease.

The surgically treated patients have been followed closely during the first years after the operation. Phrenicotomy did not fulfil expectations. Three cases on whom resections were carried out were almost free of symptoms. There were no operative deaths. One patient died later from leukaemia. The results of the herniotomies have been reported previously in other papers from this hospital (Husfeldt, Thomsen & Wamberg 1951, and Husfeldt 1953). In the present follow-up of the whole series of 34 cases submitted to herniotomies, 15 patients still had a hernia on radiological examination. 7 of these had symptoms while 8 had only trivial complaints or none at all. We realise that the group "sliding hernias with pathological changes in the oesophagus" may comprise cases of Barrett's "congenital short oesophagus" as an oesophagoscopy was not done in all cases. The diagnosis "congenital short oesophagus" can only be made when both thoracotomy and oesophagoscopy are performed.

Discussion

The higher incidence of hiatus hernia in children is explained by the fact that radiological examination of the oesophagus and the stomach has come into current use in unexplained cases of regurgitation and vomiting in infants. The dominating factor in the disease is regurgitation which leads to oesophagitis. The primary aim of the treatment must be to prevent regurgitation, either through the conservative measures mentioned above or by surgery attempting to reestablish the normal function of the cardia.

In our experience conservative measures in treatment of sliding hernias in infants are not inferior to operative treatment in this age group. Severe peptic oesophagitis as a complication of a hiatus hernia will very much reduce the chances of a successful outcome. The oesophagitis leads to fibrosis, stenosis, shortening of the oesophagus and increased regurgitation, and a curative herniotomy will be more difficult to perform. If regurgitation is not brought to a stop the oesophagitis will be progressive. A severe stenosis may often result. This may diminish the regurgitation without any serious consequences apart from the necessity of eating a liquid or semiliquid diet.

As the results of herniotomy have not been satisfactory we are now of the opinion that operative treatment of strictures of the oesophagus caused by regurgitation must be a resection. Resection of the cardio-oesophageal angle means that any rest of sphincteric action is sacrificed. Regurgitation may be a serious complication after resection (Sweet *et al.*, 1954). In children resection is presumably best carried out as a high resection of the oesophagus and with the anastomosis performed between the oesophagus and the stomach through a right-sided thoracotomy.

Conclusion

According to our experience the choice of treatment should be decided upon according to the following principles:

Small infants with sliding hernias should be treated conservatively as oesophageal changes are seldom present at this early stage. In many cases this will allow complete recovery.

As comparatively few cases are diagnosed after the age of 2 years (Carré et al., 1951), a number of spontaneous cures must occur.

Children aged 2–6 years with sliding hernias but without pathological changes in the oesophagus should be subjected to a herniotomy in order to prevent these changes occurring.

Most cases of sliding hernias accompanied by oesophageal changes cannot be treated successfully by a simple herniotomy and this is especially true in cases of stenosis. An oesophageal resection is a major procedure and carries a rather high mortality. In our experience children with stenosis may do quite well if properly cared for. Resection should be postponed as long as possible and only be carried out if conservative measures definitely fail.

All cases of paraoesophageal hiatus hernia require operative treatment. These hernias are generally large and may compress neighbouring organs in the thorax or else the herniated part of the stomach may incarcerate or develop an ulcer.

Summary

Sixty-three cases of hiatus hernia in children are presented. The diagnosis is discussed with special reference to radiological examination. 34 children were submitted to 45 operations. 29 children were treated medically. The results of the treatment given are analysed.

Hernie de l'hiatus de Winslow chez des enfants.

Description de 63 cas de hernie de l'hiatus de Winslow chez des enfants. Discussion du diagnostic avec référence spéciale à l'interprétation des données radiologiques. 34 enfants ont été soumis à 45 opérations. Les 29 autres ont fait l'objet d'un traitement médical. Les auteurs donnent une analyse des résultats des traitements appliqueés.

Hiatushernie bei Kindern.

63 Fälle von Hiatushernie bei Kindern werden angeführt. Die Diagnose wird mit besonderer Berücksichtigung der röntgenologischen Untersuchung erörtert. 45 Operationen wurden an 34 Kindern durchgeführt. 29 Kranke wurden konservativ behandelt. Die Ergebnisse der Behandlung werden analysiert.

Hernia hiatal infantil.

Preséntanse los casos de 63 niños afectos de hernia hiatal. Discútese el diagnóstico especialmente con referencia al examen radiológico. 34 niños fueron sometidos a 45 operaciones. 29 niños fueron sujetos a tratamiento médico. Analízanse los resultados producidos por el tratamiento.

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Syndrome of the Anterior Spinal Artery

by BERTIL LINDQUIST

The clinical picture of the syndrome of the anterior spinal artery is characterised by sudden paraplegia or tetraplegia, anesthesia as well as disturbed bladder and bowel function. Trophic disturbances are also common. As in syringomyelia, the anesthesia is of dissociated type, i.e., loss of perception of pain and temperature with preservation of the sense of touch, vibration and position. The clinical picture is attributable to a lesion of the spinal cord in some segments supplied by the anterior spinal artery and its branches. This clinical picture was first described in 1904 by Praeobrajensky. In 1936 Zeitlin and Lichtenstein gave a survey of cases on record. Some of them had been verified at autopsy. The syndrome, is, however, so characteristic that the diagnosis can, as a rule, be established clinically. Paine and Byers (1953) described 25 cases of transverse myelopathy in children, 10 of whom showed a clinical picture coinciding with that of the syndrome of the anterior spinal artery. However, the syndrome appears to be rare in children.

The understanding of the symptoms will be facilitated by a brief description of the blood supply to the medulla (see Suh & Alexander 1939, Herren & Alexander 1939).

The anterior spinal artery is formed by the union of a branch given off by each vertebral artery before the latter joins the basilar artery. These two branches unite at a level roughly in the middle of the cervical region, and the common artery—the anterior spinal artery—then runs down the anterior surface of the spine in the anterior median sulcus. From the middle of the cervical region and downwards blood is received from branches of intercostal, lumbar and sacral arteries which reach the spinal cord along its anterior roots (radicular arteries). Wide variations are, however, seen in this anatomical topography; sometimes certain spinal arteries are strikingly large in relation to the others. The anterior spinal artery supplies mainly the anterior part of the medulla. The posterior part, on the other hand, is supplied by two arteries extending along the posterior surface of the medulla. The main branch of the anterior spinal artery is the central sulcus artery, which penetrates the grey substance on either the left or the right side of the cord.

A lesion of the spine in the region supplied by the anterior spinal artery will lead to injury of the grey substance in the anterior horns and, among other things, of the pyramidal tracts and the spinothalamic tract. This causes both motor and sensory disturbances. The motor disturbances comprise, above all, paresis of a limited area in the musculature, corresponding to injury of the anterior horn cells. In addition, simultaneous injury of the pyramidal tracts will produce spastic paresis of the musculature, whose nerves have their motor cells in the anterior horns below the level of the lesion of the spinal cord. The symptoms naturally vary with the level of the lesion. In the most typical cases, with the lesions in the cervical portion of the spine, flaccid paresis is seen in the upper extremities or parts of them and spastic paresis in the lower extremities. Sensory disturbances are, as mentioned, of dissociated type, i.e., the sense of touch is unimpaired, while the perception of pain and temperature is lost. The sense of touch is preserved as it is mainly conducted by the posterior tracts which have a different blood supply.

Post-mortem examination shows a softening of the spinal cord, a myelomalacia.

In the aetiology of the syndrome vessel injuries play an important role. Syphilis has been described as a common cause, and arteriosclerosis has been demonstrated in some cases in older patients (Hassin). Indirect violence has also been suggested as a cause of the syndrome (see below). In some cases in children it has been ascribed to infection (Paine & Byers). In other cases no acceptable explanation could be offered (Ornsteen 1931).

In view of the anatomical changes in the spinal cord the prognosis of the syndrome is poor. This applies above all to older patients, in whom the cause is often arteriosclerosis. In young patients the prognosis appears to be more favourable.

Below a report is given of a case of the syndrome of the anterior spinal artery. This case appears to be the first seen in childhood with the classical syndrome including involvement of both the upper and lower extremities.

Case Report

History.—The patient was a boy, aged 6, who had hitherto been healthy. Inquiry into the familial history revealed nothing of interest. On the morning of April 30, 1948, the boy had been out in a barn playing by himself. When he came indoors the mother noticed that he appeared tired and the boy sat down in a chair. At that time no signs of paralysis were observed. The mother went upstairs to fetch a rug and came down again after 5–10 minutes. In the meantime the child had laid down on a sofa, he was unable to grip with the right hand, and after a few minutes he could not grip

with the left hand either. The paralysis then spread rapidly and after half an hour to one hour he had total paresis of both arms and legs and could not sit up in bed without support. Otherwise he appeared to be unaffected—he talked and laughed as usual. He did not complain of headache or nausea, but had mild stomach-ache.

The boy was admitted to a Hospital for Epidemic Diseases on May 1, because of suspected poliomyelitis. On admission both arms and legs were paralysed, as was the bladder and the bowel. The left pupil was enlarged, but reacted to light. He was in a good general condition, he had no neck stiffness, and Lasègue's sign was negative. The region over the spine was not tender to palpation. Repeated lumbar punctures showed no signs of a pathologic condition, and Wasserman's test was negative.

On May 12 the patient was transferred to a medical department. He still had paralysis of both legs. A certain degree of spinal automatism had, however, developed. The condition of the arms showed some improvement: he could lift them, but the hands were still completely paralysed. The paralysis of the bowel and bladder persisted as before. The tendon reflexes of the arms, the patellar and the Achilles reflexes could not be elicited on either side. The abdominal reflexes were also absent, and Babinski's sign was positive on both sides. The sense of touch was unimpaired, but perception of temperature was doubtful. Radiographs of the cervical spine showed no signs of a pathologic condition. The patellar and Achilles reflexes as well as the tendon reflexes of the arms gradually returned. The patient was also gradually able to move his arms and legs.

On admission on August 23, 1948, the patient was in a good general condition. He was mentally clear and gave reasonable answers, although it was difficult to establish rapport with him. The lower legs were moderately oedematous. In both gluteal regions were some ugly sores. Bowel and bladder paralysis persisted and he lay with a catheter à demeure. Abdominal palpation revealed nothing of interest.

Neurologic examination.—The tendon reflexes of the arms were normal. The patellar and Achilles reflexes were very marked, the latter with persistent clonus bilaterally. The abdominal and cremasteric reflexes were absent, and Babinski sign was positive on both sides. The sense of touch—examined with cotton wool—was normal all over the body. Perception of temperature was unimpaired on the face, arms, neck and upper part of the chest down to the level of the mamillary plane, below which it was completely absent. The sense of pain—tested by power of differentiation between the point and head of a pin—could not be determined on admission, because at that time, the patient could not be persuaded to co-operate. As to the motor disturbances, both legs could be actively bent and lifted from the bed but only with extreme exertion, and the patient could not stand, not even with support. There was marked spasticity of both legs. No muscle atrophy could be demonstrated. The gross functional power of the arms was good with the exception of the hands, where strength was severely impaired. Thus, he could not bend the distal finger joints. The proximal digital joints in the third, fourth and fifth digits of the left hand could be bent even against some resistance. The corresponding capacity of the right hand was negligible. The motility of the thumb and the second digit on each hand was practically nil.

Laboratory findings.—The blood picture was normal. Lumbal puncture revealed nothing of interest. Skull x-ray and radiographs of the neck, chest and lumbar region showed no signs of a pathologic condition. Encephalography showed no abnormality. Oxygen myelography (O. Ohlsson): "the entire subarachnoid space is patent. The spinal cord is of ordinary thickness and position throughout".

Course.—The patient gradually but steadily improved, and some months after

admission he was able to support himself on his legs with a help of walking trestles. Bladder and bowel function began to return and automatism developed.

Six months after admission the neurological condition was as follows: The gross functional power of the hands was still markedly decreased. The strength of both thumbs was impaired with complete loss of function of the opponens. The functional capacity of the other fingers was markedly decreased on the right hand, but not so markedly on the left. The muscles of the thenar eminence had undergone marked bilateral atrophy. In addition, there was moderate atrophy of the musculature of the palm on the right side. Perception of temperature was still absent below the mammillary plane. It was now possible to persuade the patient to co-operate in the examination of the sense of pain. It was found to be unimpaired in the face and on the arms, but decreased in the legs and the trunk—it was, however, not possible to definite the border exactly. The sense of touch was unimpaired as before. The abdominal and cremasteric reflexes had returned, but the patellar and Achilles reflexes were still spastic. Babinski's sign, Oppenheim and Gordon were positive bilaterally.

After a further six months the motility of the arms and hands was, generally speaking, unchanged as was the atrophy of the hands. A certain further improvement of the lower extremities was noted; the patient could now walk on crutches and for short distances with a walking stick only. The sensibility was as before. Considerable improvement was, however, noted in the function of the bladder and bowel, so that he was now continent.

Recapitulation.—The spread of the symptoms thus suggested that the lesion was located at the level of the lowermost cervical and uppermost thoracic segments, where it involved mainly the anterior part of the medulla.

Discussion

Myelopathy with symptoms resembling those seen in the case described above which occur in association with or after infectious diseases are usually regarded as being of infectious nature, i.e., as transverse myelitis. This was accepted as the origin in 6 of 10 cases of anterior spinal artery syndrome in childhood in Paine & Byer's series. In the case described above, there was no history of a preceding infection. The absence of pathologic findings in the cerebral spinal fluid and the absence of signs of a transverse lesion also argue against a diagnosis of myelitis.

Medullary tumours usually obstruct the circulation of the spinal fluid which gives rise to typical symptoms, the so-called Froin's compression syndrome. In the present case the patient showed no such signs. Oxygen myelography, as well as the favourable course argue against intraspinal tumour being the cause of the condition.[1]

A striking feature of the clinical picture of the patient in the present case was the very acute and dramatic onset of the symptoms. This suggested a vascular lesion as a cause of the syndrome. Such a lesion may consist of

[1] On a follow-up examination of the patient 1954 his condition was practically unchanged.

bleeding in the medulla, a haematomyelia, or occlusion of the anterior spinal artery, and it is sometimes difficult if not impossible to differentiate between these two conditions. The absence of red blood cells in the cerebrospinal fluid argued against hemotomyelia. Furthermore, haemotomyelia is often located centrally, and the clinical picture is usually represented by the so-called central syndrome, in which one of the more typical traits is a segmental limitation of sensibility disturbances both above and below (Hassin). Bleeding in the medulla need not, however, be limited to any particular region, but may occur in both the grey and white matter. Haemorrhage in a tumour will also explain the acute onset of the symptoms. As mentioned, however, there was probably no tumour. Haemorrhage in a vascular anomaly must also be considered. Such anomalies in children have been described by Buchanan and Walker (1941).

As mentioned, a vascular lesion can also result from an occlusion (thrombosis or embolism) of the anterior spinal artery. At this level, i.e. between the cervical and thoracic segments, the vessel supplies the anterior two thirds of the medulla. The clinical picture also agrees well with that of earlier cases described in the literature and verified at autopsy. Grinker and Guy (1927) described such a case. The patient was a boy, aged 15, who, on one occasion, yawned strongly, with his arms extended backwardly and upwardly. A few hours later he complained of weakness of the arms and shortly afterwards of the both legs. He had analgesia and thermoanesthesia below C_4 but the sense of touch was unimpaired. Atrophy of the small muscles of the hand and of some of the muscles of the lower arm was analysed. Paresis of the lower extremities was flaccid. However, the patient only survived one month. Autopsy revealed a thrombus in the anterior spinal artery and myelomalacia in the anterior part of the medulla at a level of C_{4-6}. The injury was ascribed to temporary luxation of the fifth cervical vertebra, resulting from an over-extension of the cervical spine in connection with the strong yawning (see above), with a secondary compression of the anterior spinal artery followed by thrombosis of the vessel. Paine and Byers expressed the view that many cases of so called acute transverse myelitis are of vascular origin, often due to thrombosis of the anterior spinal artery. In our case it is not possible to find any factors favouring the development of any vascular injury. There was no reason to suppose embolism—the patient had a healthy heart. No signs of vascular or blood disease were noted.

The possibility of traumatic origin in our case cannot be excluded, because just before the onset the boy was playing in a barn by himself. Indirect violence has been assumed to be the cause of the syndrome in a case described by Grinker and Guy (see above) and in another case described by Spiller (1909). In the latter case the first signs of paralysis appeared 15

minutes after the patient had lifted a heavy block of ice. A typical syndrome then developed with flaccid paresis of the upper extremities and spastic paresis of the lower extremities. The patient also had dissociated impairment of sensibility and impaired bladder and bowel function. Autopsy revealed occlusion of the anterior spinal artery with a change in the vessel wall probably due to syphilis and myelomalacia in the region C_4-T_3. In one case described by Stone and Roback (1937) the syndrome developed after the patient had climbed up a tree. The clinical picture in their case was, however, atypical, suggesting injury of the entire segment, which was also confirmed at autopsy.

The course of the syndrome in question has been described as fairly favourable in young people. Of Paine & Byer's 10 cases of the syndrome improvement or recovery was noted in 5. The improvement of one of Steegmann's (1952) cases with the anterior spinal artery syndrome was remarkable: the patient was a girl, aged 14, with signs of lesion of the lower thoracic region, and the symptoms disappeared completely within 3 weeks. It is true that in the present case the clinical picture changed only slowly but an appreciable improvement has been noted. Some of the injuries are, of course, irreversible, so that a certain degree of permanent invalidism must be expected.

Summary

A case is observed of the anterior spinal artery syndrome in a boy aged 6. Paralysis developed within half an hour with tetraplegia followed by dissociated anesthesia and loss of bladder and bowel function. The symptoms were probably due to a vascular lesion, possibly because of trauma. This is apparently the first report of the classical picture in a child.

Le syndrome de l'artère spinale antérieure.

Description d'un cas de syndrome de l'artère spinale antérieure chez un garçonnet de six ans. La paralysie s'est installée en une demi-heure avec une quadriplégie suivie d'une anesthésie disociée et d'un arrêt du fonctionnement de la vessie et des intestins. Ces symptômes étaient probablement dûs à une lésion vasculaire provenant sans doute d'un traumatisme. Il semble que ce soit là le premier cas présentant la symptomatologie classique qui ait été observé chez un enfant.

Das Syndrom der vorderen Spinalarterie.

Beschreibung eines Falles mit vorderem spinalen Arteriensyndrom bei einem 6-jährigen Knaben. Lähmung trat innerhalb einer halben Stunde ein mit Tetraplegie und war von einer dissoziierten Anästhesie und Verlust der Blasen- und Darmfunktion gefolgt. Die Symptome waren wahrscheinlich durch eine, möglicherweise traumatisch bedingte Gefässbeschädigung verursacht. Das ist anscheinend der erste Bericht eines klassischen Krankheitsbilds bei einem Kinde.

El sindrome de arteria espinal anterior.

Obsérvase el caso de un niño de 6 años de edad, presentando el sindrome de arteria espinal anterior. La parálisis se desarrolló en el espacio de media hora, con tetraplegía seguida de anestesia disociada y pérdida funcional de la vejiga y de los intestinos. Los síntomas probablemente se debieron a una lesión vascular, posiblemente originada por un trauma. Aparentemente es esta la primera vez que se consigna el sindrome clásico con relación a un niño.

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Probenecid-Penicillin Allergy

Allergic Mucocutaneous Reactions Following Treatment of Haemolytic Streptococci Infections with Penicillin Preparations Containing Probenecid

by JUSTUS STRÖM

Reports of allergic reactions to penicillin treatment have become increasingly common, particularly in the United States. This is attributed—no doubt rightly—to the extremely extensive use and abuse of penicillin which has gradually sensitized increasing numbers of people.

Hypersensitivity reactions occur after every form of penicillin administration, though the parenteral route is more hazardous than the oral. In the comprehensive trial series of scarlatina cases treated with different forms of penicillin, conducted at the Stockholm Hospital for Infectious Diseases over a period of ten years, the side-effects of the penicillin therapy have been very infrequent. Cases of exanthemata, however, and, in particular, fever reactions were observed after injections of long acting DBED-penicillin (Ström & Tunevall, 1955).

The reactions to oral administration—in the last few years principally of penicillin-procaine—have hitherto been very rare. But new forms of oral penicillin therapy have been introduced. The means of raising and maintaining the concentration of penicillin in the blood were found in the product probenecid, which inhibits the renal excretion of penicillin. At the same time the search for forms of penicillin with greater resistance to the gastric hydrochloric acid was crowned with success in the advent of phenoxymethyl penicillin (penicillin V). Increasingly efficient oral preparations have been developed through the combination of different types of penicillin with probenecid. The present paper is an account of trials undertaken in 1956 for the treatment of scarlatina with various new penicillin preparations, not so much in relation to the effect of the therapy—which was usually satisfactory—but to the observed reactions to these preparations.

Material and Methods

Four different kinds of tablets have been used:

1. Benzyl penicillin potassium (Penicillin G) (Astra).
2. Benzyl penicillin potassium + probenecid—Probecillin (Astra).
3. Phenoxymethyl penicillin (Penicillin V)—Meropenin (Kabi).
4. Phenoxymethyl penicillin potassium + probenecid—Vebecillin (Astra).

Concentrations have been 100,000 and 250,000 international units of penicillin with, in the probenecid preparations, 0.25 and 0.50 g respectively of probenecid per tablet.

In a department for patients with diseases caused by haemolytic streptococci (scarlatina in acute stage, scarlatina in desquamation stage, other streptococcal diseases) alternate cases were treated with tablet 1 and tablet 2; and in another department likewise with tablets 3 and 4. Thus four concurrent series have existed. The period of treatment was 14 days. Identical doses were given to all series as set out below:

Age (years)	Penicillin (all 4 series)	Probenecid (Probecillin and Vebecillin series)
0	50,000 I.U. × 2	0.125 × 2
1–4	100,000 I.U. × 2	0.25 × 2
5–9	150,000 I.U. × 2	0.375 × 2
10–14	200,000 I.U. × 2	0.50 × 2
15–	250,000 I.U. × 2	0.50 × 2

Results

Rashes occurred in a large number of patients treated with probenecid-penicillin preparations, but not in those who received the same penicillin preparation without probenecid. The general reactions and discomfort of patients were slight. One day, however, a severe pathological picture was observed in a patient receiving the combined treatment, and the two probenecid series—despite the original intention that each series should continue until it numbered one hundred scarlatina patients—were broken off. The very low number of cases in the Probecillin series was because admissions to the smaller department could not be maintained at the same rate as in the other.

Table 1 shows the results of the probenecid–penicillin cases. The other two series, of one hundred scarlatina patients each, contained no side-effects whatsoever.

The reactions were extremely numerous. All cases manifested exanthemata. The Vebecillin cases were more numerous than the Probecillin cases in each pathological group. Statistical significance exists both between the percentages of the total materials (diff.: $39.2\% - 15.7\% = 23.5\%$; $P < 0.01$)

TABLE 1

Disease	Cases treated	Cases with exanthema				Site of mucous sympt.			
		Tot.	%	With fever	With muc. sympt.	Conj.	Mouth, throat	Gen.	Anus
Vebecillin									
Scarl. ac. stage	74	33	44.6	26	15	15	3	3	2
Scarl. desquam. stage . .	23	9	39.1	8	2	2	—	—	—
Other strept. dis.	23	5	21.7	4	1	1	—	—	—
Total	120	47	39.2	38	18	18	3	3	2
Probecillin									
Scarl. ac. stage	45	9	20.0	4	5	5	1	—	—
Scarl. desquam. stage . .	12	1	8.3	1	1	1	—	—	—
Other strept. dis.	13	1	7.7	—	—	—	—	—	—
Total	70	11	15.7	5	6	6	1	—	—
Vebec.+Probec.	190	58	30.5	43	24	24	4	3	2

and between the percentages of the scarlatina groups (diff.: 44.6% – 20.0% = 24.6%; $P < 0.01$). The mucous membrane affections attendant upon exanthema have also been somewhat more numerous in the Vebecillin than in the Probecillin groups. A remarkable thing is the falling tendency in the incidence of reactions from scarlatina in the acute stage through scarlatina in the desquamation stage to other streptococcal diseases. The difference between scarlatina and other streptococcal diseases in the grand total shows quite a high degree of probability (diff.: 35.3% – 16.7% = 18.6%; $P = 0.035$).

Fever occurred in 80 per cent of the Vebecillin cases. Temperatures were mainly fairly low, and a temperature above 38° was recorded only in half of the cases. In nine of the thirty-eight cases, however, it was above 39°, the maximum temperature being 40.7°. The duration of the fever was normally 1–5 days, max. 11 days, mean 3.8 days. The fever reaction was less pronounced in the relatively small number of cases in the Probecillin series.

The time of onset of reactions is shown in Fig. 1. The incidence for exanthema was highest on the 8th and 9th days (earliest 6th, latest 14th). Fever often occurred 1 to 2 days before the exanthema (28 out of 38 cases) or simultaneously with it (9 out of 38), only on one occasion on the day after.

Clinically the general status was usually very slightly affected. There were no sequelae deriving from heart or kidneys. The exanthema, which

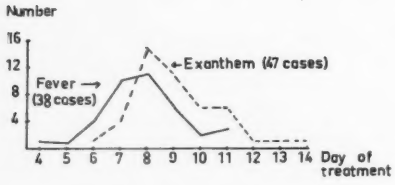

Fig. 1. Onset of fever and exanthema in Vebecillin-treated cases.

occurred in all 58 cases of reactions, consisted of urticaria in six patients and of maculopapular forms in the remainder. In four cases the efflorescences developed in circinate form, and in one case as bullous eruptions. The efflorescences were generally of pea to bean size, but there were considerable variations. The colour varied from light to dark red with a tendency in more pronounced cases to become strongly bluish-red. In two thirds of the cases eruptions were found both on trunk and extremities, in the re-

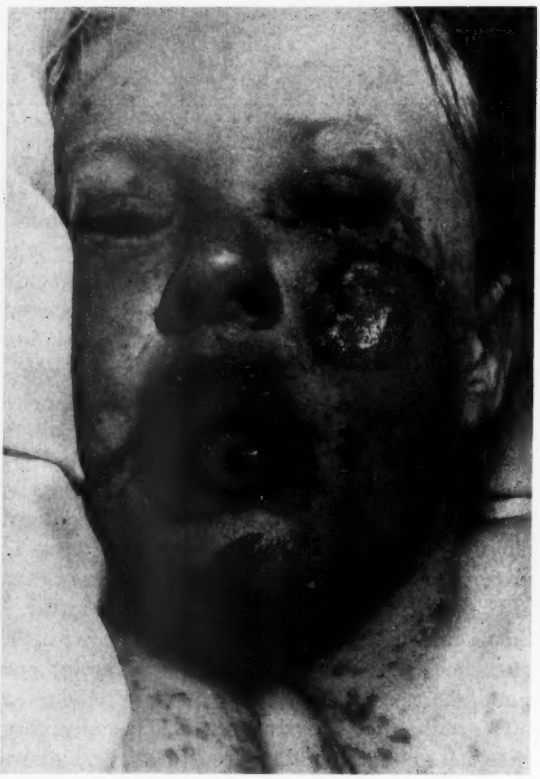

Fig. 2. Pat. E. H. Vebecillin-treated case with mucocutaneous syndrome.

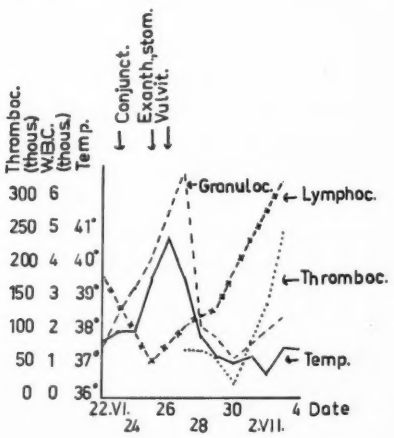

Fig. 3. Pat. E. H. Onset of clinical symptoms and blood picture.

mainder either on trunk or extremities. In half of the cases there was a marked symmetry in the arrangement. The rash usually disappeared at the same time as the fever.

Among the mucous membrane reactions conjunctivitis was most common, being usually of moderate severity; the mouth and throat affections consisted usually of enanthema on the inside of the cheeks and in the throat; and affection of the genitals consisted of vulvitis or balanitis, in one case with ulceration. Blotchy redness and swelling occurred around the anus, and in one case erosions. The severely attacked case described below developed the entire picture of high fever and a violent skin and mucous membrane affection of bullous and pseudomembranous type (Fig. 2).

Case no. 2603/56. E. H., female, 7 years. Pneumonia 1953, otherwise healthy. Hospitalized for scarlatina on June 11, 1956. From June 12 Vebecillin 150,000 I.U. × 2. June 23: temp. 37.4–38°, irritation of the eyes. June 25: temp. 38.5–39.6°, eyes swollen, severe conjunctivitis, lips swollen and cracked, isolated maculopapules on neck and forearms. June 26: temp. 39.8–40.7°, affected, chilliness, listless, vomiting; maculopapular and vesicular rash on face, also on trunk; gingivitis and glossitis, smarting during urination, severe redness of vulva and around anus. Treated by intravenous drip, antihistamine, calcium intravenously followed by ACTH and erythromycin intravenously.

The condition improved fairly rapidly, the fever dropping to 39° on June 27, and after June 29 the patient was afebrile.

The eruption was widespread, bullous and haemorrhagic. The stomatitis was severe, with coating of the whole mouth and crusted lips (Fig. 2). Ulceration occurred in the vulva and around the anus. The blood picture (Fig. 3) first showed a tendency to leucopenia (June 25–5, 300), thereafter moderate neutrophil leucocytosis accompanied by lymphocytopenia and pronounced thrombopenia (down to 20,000). Lungs, kidneys, heart: normal.

Discussion

The probenecid-penicillin preparations used in this study have thus produced an extraordinarily high incidence of side-effects, far higher than would have been expected from the knowledge possessed of the allergic reactions provoked by the two drugs independently. Feinberg & Feinberg, in J.A.M.A. 1956, present a survey of penicillin allergies. Apart from a number of cutaneous reactions they also mention the possibility of periarteritis nodosa and lupus erythematosus. Most significant, however, are the immediate anaphylactic shock and the delayed serum sickness type. It is estimated that several hundred patients die of shock every year in the U.S.A. (Welch *et al.*).

The trials reported in this paper, however, refer exclusively to delayed reactions following on oral therapy. An idea of the incidence of such reactions may be obtained from a study made by Berry & Ferber in 1954. They treated no less than 33,827 airmen prophylactically against streptococcal infections with 250,000 I.U. of crystalline penicillin by mouth three times a day in different groups for five and ten days respectively (23,495 men for 10 days). Only 90 persons (0.27 per cent) had reactions, of which 38 (0.11 per cent) were delayed.

What then are the allergenic properties of probenecid? This drug has come into quite extensive use, not only in penicillin therapy, for which it was originally produced, but also for gout and PAS treatment of tuberculosis. Thus a quite considerable experience of prolonged treatment with pure probenecid is available. Boger & Strickland, in 1955, made a survey of the use of probenecid and its side-effects in no less than 2502 cases. The toxicity was very slight. Hypersensitivity reaction was observed in only 8 cases (0.31 per cent), drug fever in 9 cases (0.36 per cent), and skin rash in 34 cases (1.35 per cent). "In at least five of these patients probenecid was being administered in conjunction with penicillin."

Compared with these investigators' experiences of delayed reactions to penicillin and probenecid, the side-effects in our trials were on a vastly greater scale, even if their figures of the reactions to the two drugs are combined.

In our trials the control series, who received only benzyl penicillin potassium and phenoxymethyl penicillin, suffered no side-effects. The cause cannot, therefore, be attributed to these preparations. Intracutaneous testing against benzyl penicillin in 16 cases with reactions has shown no hypersensitivity. Notwithstanding, penicillin must be of considerable significance in this connection. We have here a statistically proved difference in the incidence of reactions to the two probenecid-penicillin preparations.

If the cause is the higher penicillinaemia, which phenoxymethyl penicillin produces, or this special type of penicillin can not be answered by this investigation.

Nor can probenecid in itself be blamed for the unhappy effect. This is *a priori* improbable owing to earlier experience of its allergenic properties. The trouble must lie in the unusually unlucky combination of drugs.

A further question arises. How can it be possible that this marked tendency to side-effects has not been observed earlier, seeing that Probecillin, at least, has been available for some two years and has been much used in practice? It cannot be a question of dosage, since in these trials the doses have been maintained at the recommended level. Can the nature of the illness have been a factor? Manifestly it may. Statistically there is a fairly high degree of probability that the incidence of allergic reactions is greater in acute scarlatina than in other infections caused by haemolytic streptococci. This may perhaps be explained by the capillarotoxic effect that manifests itself in the disease. The question is whether streptococcal infections do not in fact favour the occurrence of allergic reactions. My experience of such reactions with severe mucocutaneous manifestations supports this view. Boger stated in 1954 that the incidence of rashes as a result of combined penicillin and probenecid therapy was as low as 1.2 per cent. The incidence in this material of haemolytic streptococcic infections is incomparably higher (16.7 per cent).

There is reason to pay attention to yet another circumstance. There is a delayed reaction which, in accordance with what has been shown here, seldom appears until after six days of treatment, with maximum after eight or nine days. This must be another reason why side-effects are not so often observed in practice.

These studies have produced a further very important result. A gradually rising succession of allergic reactions is found from exanthemata alone, through exanthemata accompanied by fever, to, finally, a combination with mucous membrane reactions. The severest forms are, among others, those which are known under the name of Stevens–Johnson syndrome or Ectodermosis erosiva pluriorificialis. There is considerable uncertainty concerning the cause of these syndromes, but in an earlier paper I stated as my view that the syndrome is of allergic origin, of which the present paper provides distinct evidence.

Summary

In the use of probenecid-penicillin tablets for the treatment of scarlatina in the acute stage and in the desquamation stage, and of other diseases caused by haemolytic streptococci, side-effects occurred to a considerable extent. On the other hand, in

two concurrent series of scarlatina, each of 100 cases, treated with the penicillin types in question, benzyl penicillin and phenoxymethyl penicillin, there were no reactions.

The side-effects were of the delayed allergic reaction type. Their incidence in the total material of patients treated with probenecid-penicillin was 30.5 per cent (58 out of 190 cases). In all cases the reaction took the form of exanthema, in three quarters of the material being accompanied by fever which usually appeared one to two days before the exanthema, and in about 40 per cent by mucous membrane reactions, also in the form of Stevens–Johnson syndrome or Ectodermosis erosiva pluriorificialis. This is of the greatest interest, since it illustrates the pathogenesis of these syndromes. One severe case is described.

Penicillin and probenecid may both produce delayed reactions, but to not nearly so great an extent as related here. There must, therefore, have been an unfavourable combination of drugs from the allergic aspect. Statistical analysis of the material also shows that the incidence of allergic reactions in combined treatment with probenecid is greater in the case of phenoxymethyl penicillin than in the case of benzyl penicillin. The nature of the illness is also a factor, however, since the incidence of reactions is higher in scarlatina than in other streptococcal diseases treated in this investigation.

Probenecid-penicillin preparations should be used with caution when administered over long periods, especially in treating scarlatina.

La probénécide-pénicilline allergie

L'emploi de comprimés de probénécide et de pénicilline dans le traitement de maladies dues au streptocoque hémolytique a donné lieu à des réactions secondaires tardives dans 30,5 % des cas (soit dans 58 cas sur 190). Toutes ces réactions prirent la forme d'un exanthème accompagné de fièvre dans les trois quarts des cas et de réactions mucomembraneuses du type du syndrome de Stevens-Johnson ou de l'ectodermose érosive pluri-orificielle dans environ 40 % des cas. Le probénécide et la pénicilline peuvent tous deux donner lieu à des réactions secondaires, mais l'incidence de ces dernières est nettement plus faible que celle qui fut observée ici. Les réactions secondaires observées lors du traitement combiné avec le probénécide furent plus fréquentes avec la phénoxyméthylpénicilline qu'avec la benzylpénicilline; de même leur incidence fut plus élevée dans les cas de scarlatine que dans les autres infections streptococciques.

Probenecid-Penicillin Allergie

Bei der Anwendung von Probenecidpenicillintabletten zur Behandlung von Krankheiten, die von hämolytischen Streptokokken hervorgerufen waren, wurden Nebenwirkungen vom verzögert allergischen Reaktionstypus in 30,5 % d.i. bei 58 unter den 190 Fällen, beobachtet. Alle Fälle wiesen Exanthem auf, das in drei Vierteln von Fieber und in etwa 40 % von Schleimhautreaktionen, auch in der Form des Stevens-Johnson'schen Syndromes und der Ektodermosis erosiva pluriorificialis, begleitet war. Sowohl Penicillin als auch Probenecid können Spätreaktionen hervorrufen, aber in beiweitem nicht so hohem Ausmasse, wie hier berichtet wurde. Das Auftreten von Reaktionen bei der kombinierten Probenecidbehandlung war häufiger im Falle des Phenoxymethylpenicillins als des Benzylpenicillins, und beim Scharlachfieber als in anderen Streptokokkeninfektionen.

Probenecid-Penicillin Allergia

El uso de comprimidos de penicilina-probenecida en el tratamiento de las enfermedades causadas por estreptococos hemolíticos, provocó efectos secundarios por reacción alérgica diferida en un 30,5 por ciento (58 de los 190 casos). Todos ellos manifestaron exantema, tres cuartos de los cuales iban acompañados con fiebre y aproximadamente 40 por ciento con reacciones de las mucosas, también bajo forma del sindrome de Stevens-Johnson y de Ectodermosis erosiva pluriorificial. La penicilina y la probenecida pueden ambas provocar reacciones diferidas aunque apenas tan elevadas como las más arriba citadas. La incidencia de las reacciones consiguientes al tratamiento combinado con probenecida fué en el caso de la pencilina fenoximetílica que en el de la penicilina bencílica y fué más alta en la escarlatina que en las otras enfermedades estreptocócicas.

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Section of Pediatrics and School Hygiene of the Swedish Medical Society

Meeting October 12, 1956

L. Ström: **Hypoglycemia and its causes.**

Account of McQuarrie's work on hypoglycemia and description of one of the author's own cases. A patient, girl, 8 years old, with typical anamnesis and typical tests favouring the diagnosis idiopathic hypoglycemia, is demonstrated. Of interest in this case is the fact that during the pregnancy the mother developed a diabetes. The etiological significance of this for the child's disease is discussed.

Discussion.—*B. Hökfelt.* In the series reported by McQuarrie it is mentioned, *inter alia*, that in a pair of twins with idiopathic hypoglycemia it was not possible to show alpha cells in the pancreas. I should like to draw attention to a couple of facts that would indicate that the alpha cells, not least in the young organism, are of importance for the counteracting of hypoglycemia. Thus in the new-born individual the ratio of alpha-beta cells is 50:50, ind in the full-grown individual, on the other hand, 20:80, which probably supports the assumption that in the earlier part of life the alpha cells play an important physiological rôle. Further, it has recently been shown on rabbits (Hökfelt & Hultquist, 1956) that acute hypoglycemia after insulin—as also after BZ 55—rapidly brings about cytological changes indicating a markedly increased activity in the alpha cells (the effect upon the alpha cells of BZ 55 is probably entirely due to the hypoglycemia). The adrenal gland, too, is of great importance for the counteracting of hypoglycemia. I should also like, however, to draw attention to the fact that at birth the adrenal medulla contains chiefly noradrenalin and only an inconsiderable amount of adrenalin; in the adult individual the reverse is the case (Hökfelt, 1951). As compared with adrenalin, noradrenalin has only a weak blood-sugar increasing effect. Through the progressive development during the growing years of both the medulla and the cortex, the capacity of the adrenal gland to counteract hypoglycemia is enhanced. This may perhaps at least in part explain the well-known fact that in many cases idiopathic hypoglycemia disappears spontaneously.

Karlberg, P., Escardó, F., Cherry, R. B., Lind, J., Wegelius, C.: **Studies on the respiration of the new-born in the first minutes of life.**

As soon as possible after birth the volumes of the earliest breaths of the new-born were registered simultaneously with the thereto related changes in intraoesophageal pressure, at the same time as aeration of the lungs and the respiratory movements were followed with cineroentgen. For the registration of the volumes a mask was placed over the infant's nose and mouth. This mask was connected with a tube 35 mm in diameter to a 60-liter flask, where pressure changes caused by the infant's respira-

tions were picked up by an electromanometer. The intraoesophageal pressure changes were recorded by a second electromanometer with the help of a polyethylene catheter 1 mm in diameter introduced through the mouth, so that its tip was between the upper and middle thirds of the oesophagus. For the cineroentgen, Philips' image amplifier, which takes up to 50 pictures per second, was used. After amplification, the signals from the two electromanometers were registered on a 4-channel direct-writing recorder (Elema's mingograph). Small spikes on the fourth channel indicated each roentgen exposure.

Eleven normal new-born infants were studied during the first minutes of life. Tidal volume, intraoesophageal pressure and air-flow were recorded, and cineroentgen pictures were taken at 3 different intervals of time, beginning with the first breath. It was shown that there is a high resistance to the inflow and outflow of air in the first breaths, due to the cohesive forces, the air-way resistance and the relative lack of elastic recoil of the new-born lung. The sum of these resistance factors seems to be higher with expiration than with inspiration. This resistance decreases rapidly during the first minutes of respiration. Aeration was shown to be a progressive process.

Zetterström, R. and Berglund, G.: **Vascular hemophilia.**

Three girls with an affection resembling hemophilia but without heredity for hemorrhagic disease were examined. The patients manifested reduced capillary resistance and prolonged bleeding time, though in 2 cases the coagulation time had always been normal, while in the third case it had as a rule been normal but on some occasions prolonged. A more complete investigation of coagulation according to accepted methods showed in all cases reduced prothrombin consumption and deficiency in antihemophilic globulin. In one of the cases the bleeding time varied; it was normal for periods and much prolonged for periods. When the bleeding time was normal the amount of antihemophilic globulin was also normal, but when the bleeding time was prolonged a considerable reduction of antihemophilic globulin was observed. In another case the coagulation defect was in part but not wholly compensated by blood from a patient with typical hemophilia. The more detailed etiology of the condition is as yet difficult to analyse, but it is probably a matter of some form of atypical hemophilia.

Ernster, L. and Zetterström, R.: **Studies on the pathogenesis of kernicterus.**

The fact that kernicterus not only occurs in cases of M. haemolyticus neonatorum but also in connection with other states in which an intensive icterus appears in a new-born infant seems to indicate that a bilirubin intoxication is the primary cause of this complication. With the aim of obtaining support for this hypothesis the effect of bilirubin upon the cellular conversion of energy has been studied *in vitro*. From these investigations it has emerged that indirectly reacting bilirubin disconnects the phosphorylation from the respiration in isolated cerebral and hepatic mitochondria. The effect appears when the concentration in the medium is 15–20 mg per cent. Bilirubin has thus proved to inhibit a metabolic process fundamental for different tissues. A bilirubin acts as a cell poison when it accumulates intracellularly in sufficiently high concentration, one is probably justified in drawing the conclusion that the risk of kernicterus occurring is determined as well by the concentration of plasma bilirubin as by the degree of immaturity of the blood-brain barrier-system.

These investigations have been in part published in Nature (*178*: 1335, 1956).

DISCUSSION.—*M. d'Avignon.* At the Children's Clinic at Karolinska sjukhuset we have recently been investigating the serological conditions in infants suffering from motor disturbances. Among those who are pure spastic cases and among those having a central motor disturbance of cerebellar type with ataxia as the most prominent symptom we have not yet found signs of incompatibility. Among those infants, on the other hand, with symptoms of an extrapyramidal athetosis there occurs in a number of cases Rh-incompatibility; but it is quite striking to observe that, although we have only recently begun and have not yet examined so many cases, there seems in other cases to be an incompatibility in the A B O-system. It has subsequently been found, when the infants are admitted for treatment of their central motor disturbance, that mother and child belong to different A B O-groups and that there are in the mother's serum antibodies of so-called immune type against the child's A, B or A and B. It may thus on good grounds probably be assumed that the mechanism for the appearance of the infant's motor disturbance of kernicterus type is the same as in cases of Rh-incompatibility, only that here it has instead been a matter of such a mechanism in the A B O-system. Infants having kernicterus from another cause than prematurity and iso-immunization in the Rh or ABO systems may also develop damage of kernicterus type. Thus we have seen a case of congenital hemolytic anemia with microspherocytosis that developed extrapyramidal symptoms.—*K. Kaijser.* Mr. Zetterström mentioned that bilirubinemia with damage of kernicterus type have been observed after the administration of certain medicaments, such as a strong dose of K-vitamin, gantrisin etc. There was no mention, however, of any such effect of other sulfa preparations or antibiotics. A premature that some days after birth becomes icteric and ailing, or whose condition only becomes worse without becoming icteric, is not infrequently treated with some of the numerous sulfa preparations or antibiotics of which so many are now available, with the idea that the worsening of the child's condition is due to infection. This is of course often the case, and often the infant's condition is improved. There is reason, one imagines, to exercise care in the choice of preparation. I should like to ask Mr. Zetterström if he has any information concerning the risk of an occurrence of kernicterus in connection with the use of other similar preparations than precisely the gantrisin mentioned by him.

Arnhold, R. and Zetterström, R.: **Functional immaturity in new-born infants of mothers with diabetes.**

Although the weight at birth is generally relatively high, infants of mothers with diabetes are often born before full term. It is therefore quite natural that these infants should show certain symptoms of immaturity, i.e. that they should in many respects appear as prematurely born children. It is also well known that the so-called hyaline membrane syndrome occurs with relatively high frequency in this group of infants. A more detailed analysis of the degree of functional maturity has shown, however, that there is often a higher degree of immaturity than can be due only to a shortening of the pregnancy. The infants of diabetic mothers who are born 3 or 4 weeks before full term are in certain respects just as immature as other infants born after only 30–32 weeks of pregnancy.

Deficient capacity to excrete bilirubin often leads to a pronounced icterus neonatorum, which also, as is the case with really premature infants, attains its maximum intensity relatively late in the new-born period. Frequently, too, the protein concentration in the liquor is exceedingly high, probably due to the fact that the blood-brain

barrier system is insufficiently developed. The often simultaneous occurrence of pronounced bilirubinemia and the undeveloped state of the barriers between the blood and the central nervous system imply a great risk for the occurrence of kernicterus. Probably the frequently occurring hypoxemia further increases the risk of this complication. A further symptom of functional immaturity is seen in the incapacity to maintain a normal calcium-phosphate equilibrium in the plasma. The tetanus-like syndrome often observed in these infants appears to be due to a hypocalcemia combined with simultaneous hyperphosphatemia. As the condition of starvation seems to accentuate this change there seems reason to consider whether it is desirable to let these infants starve, as is often done, for the first twenty-four hours of life. Still another symptom of immaturity is an incapacity completely to metabolize the amino acids phenylalanine and tyrosin. The more detailed causal connection between the mother's diabetes and the new-born infant's symptoms of immaturity is not yet clear. It appears probable, however, that the symptoms are due to a deficient development of certain enzyme-systems, possibly in consequence of hormonal influence on the fetus.

Meeting December 8, 1956

I. Alm: **Nursing frequency for premature children.**

Nursing frequency, also among Stockholm children controlled by the Child Welfare Centres, is gradually declining. At present $\frac{3}{4}$ of the children are nursed for 2 months, $\frac{1}{2}$ for 4 months and $\frac{1}{3}$ for 6 months. Of great importance of course is the way in which the nursing is started and subsequently maintained at the maternity hospitals, where nowadays almost all children in Stockholm are born. In order to judge how our technique of starting and maintaining the nursing by manual pumping 5 times daily functions, I have compared 2 series of premature infants with children ≤ 2000 g who have been discharged from premature departments of different type. The advantage of such material is in this case that all the children are separated from their mothers and transferred to special departments. It is then a matter of at least 2–8 weeks before the children can be put to the breast, and the mother gets the normal incitement of psychological and mechanical nature provided by the close contact with the child. The Allmänna Barnbördshuset (*ABBH*) denotes a premature department now nearly 40 years old and comprising 4 rooms and 10 beds for children and 4 for mothers. It is situated in the same building as an independent maternity hospital. It accepts only premature infants from this hospital, which has 2700–3000 deliveries per annum, including about $\frac{2}{3}$ from Stockholm County and $\frac{1}{3}$ from the City of Stockholm. The physician attached to the department is pediatric consultant to the obstetric departments. The mothers are moved to the premature department after 7–9 days, in which connection controls are carried out to see that they can manage the milking and that they have sufficient quantities of milk before their discharge. During these days they also have a certain contact with their children, after which daily contact is kept up until they are once more admitted to nurse the infants, which occurs when the infant weighs 2000 g.

The *Sachs Children's Hospital* has an ultra-modern premature department opened in 1950 with 20 beds for infants and 8 for mothers. It is situated in the top storey of the hospital. This is located near a general hospital with an obstetric clinic which has between 3500 and 4000 deliveries per annum but takes prematures from other obstetric departments in Stockholm too. The physician attached to the premature

department is assistant house-physician at the children's hospital and has rather little contact with the obstetric departments. The mothers are discharged by the obstetricians, after which the mothers contacts the children's hospital. They have proved to be very reluctant to move in until the infant is put to the breast, when it weighs about 2100 g. Probationers are trained at this department. The same physician has since 1945 served as pediatrician at ABBH and since 1951 as medical superintendent at Sachs.

The results are given below in tabular form.

TABLE

	ABBH, 1949–1955		Sachs, 1953–1955	
	Number	%	Number	%
Children admitted ≤2000 g	268		246	
Mortality		20.9		23.6
Discharged	212		188	
Feeding				
Breastfed		84.0		44.2
Mixed		5.6		26.6
Bottlefed		10.4		29.2
Nursing frequency				
≤1400	33	76	29	7
1410–1600	40	73	30	37
1610–1800	55	85	40	43
1810–2000	84	92	89	61
Multiparae		23.2		35.0
Born out of wedlock		28.0		27.4

Part of the great difference in the nursing frequency as between the different groups of discharged children may be explained in the light of differences in the structure of the clientèle. This applies above all to the difference between the suburban population and the urban population and the difference in the frequency of multiparas. There still remains, however, the necessity for good contact between the staff of the premature department and the mother during the whole period elapsing until the child can be put to the breast. This is more easily maintained where the premature department is situated in the maternity hospital than at children's hospitals without very close contact with the obstetric clinics supplying the infants.

DISCUSSION.—*B. Hesselman*. Gave an account of experiences at the children's department at the county hospital in Örnsköldsvik during the past year with feeding of five premature infants weighing between 990 and 1450 grams at birth. After initial starvation breast milk is supplied at first through permanent nose-catheter either as permanent drip or through instillation with syringe every 2–3 hours. When stable conditions in respect of increase of weight, body-temperature and cardiopulmonary function have been established, an attempt is made to get the infant to take milk from the

bottle, a doll's teat-bottle of plastic bought in a toy-shop being used in this connection. The results have been very favourable, and regular bottle-feeding has been possible when the infant has attained a weight of between 1180 and 1400 g. The speaker stressed the advantages of bottle-feeding as compared with probe and spoon feeding from the physiological and psychological viewpoints and as preliminary training for breast feeding, which can thus be started at an earlier stage, to the benefit of both infant and mother.

B. Söderling: **Investigations on the earliest mental development in infants.**

Studies of the infant's earliest emotional and social development, such as the first smile, the occurrence of certain conditioned sensations of pleasure and pain and the emotional and social interplay between children observed in hospital and at the ages up to 18 months. Swedish full-term infants give their first smile, statistically, on an average at the age of 4 weeks, often somewhat earlier and somewhat later, but not later than 7 weeks. To follow movements with a fixed gaze takes a further couple of weeks. Even at birth reactions of fear and pain may be observed in certain infants, in others not. The former "remember" an earlier unpleasant experience and anticipate this in the next situation in which similar conditions obtain. At the age 4 months–18 months the child has a certain need of "companions", but the contact is chiefly of a possessive, collecting type without any real fellowship or emotional engagement in the adult sense. There exists here an undifferentiated emotive plane which is difficult for adults to understand and from which emerge peaks of "ordinary" emotive manifestations such as aggressiveness, feeling of loss, vengefulness, protectiveness and need for care.

P. Karlberg, G. Klackenberg, I. Klackenberg-Larsson, H. Lichtenstein & A. Wallgren: **A study of the biological development of the child in this country.**

A. Wallgren: **Biological development of the child.**

About 15 years ago we had, practically speaking, only foreign investigations on which to base assessments of a child's development in respect of length and weight. Key's and other older investigations took account only of mean values and were too far removed in time to be valid now. But in 1940 von Sydow published his investigation on the development of infants in respect of weight, and two years later came Broman–Dahlberg–Lichtenstein's comprehensive study on development in respect of height and weight in children above infant-age. In these two investigations measurements of the height and weight attained by the child during its life to date were collected, and the distribution of these values in the group of children studied was ascertained. Another group of children at another age was then investigated in the same way, and so forth. In this way one may get a cross-section value for the height and weight for the different age-groups. For a very long time another mode of procedure has been in use. The development of one and the same child has been successively followed, what is referred to as a longitudinal or dynamic study of development. It is above all in the United States and England that this procedure has been adopted. In general it has been a matter only of studies of individual, particular attributes. In two American investigations, however, which have been carried on for more than 20 years, the child as a whole has been studied, one in Denver under Washburn and one in Boston under Stuart: the investigators have here taken a number of anthropometrical measurements, studied the mental development and the

development of the child's behaviour pattern and its adaptation to its environment. For about a year we have been carrying on a similar investigation at Karolinska sjukhuset. Our investigation is a contribution to collective research in which, besides Sweden, England, France, Switzerland, Belgium in Europe, Kentucky in the United States and French West Africa and Uganda in Africa are all represented. All the groups are carrying out the investigation in accordance with a common, carefully worked-out pattern, to enable comparisons between the children of different countries and races. The investigation is being financed wholly or in part with funds from the United Nations and is under the auspices of The International Children's Centre in Paris. Henrik Lichtenstein answers here for the somatic and social development, Gunnar Klackenberg for the mental and functional development, while Petter Karlberg is in charge of matters of registration and is responsible for the investigation in its entirety. The working team includes, besides the physicians mentioned, a children's psychologist, a social curator and a nurse.

P. Karlberg and H. Lichtenstein: **The outline of the recruitment and the physical part of the study.**

Every fourth expectant mother attending the ante natal clinic in Solna (North Western part of Greater Stockholm) has been asked if she wants to take part in our Growth study, and almost all of them have agreed. Up to now 130 children have been enrolled, and at the end of 1957 about 200 will be recruited. The social grouping of these families corresponds very well with the social groups of Greater Stockholm. The first contact with the mother is taken by the psychologist 2 months ahead of calculated date of birth. Next interview is made in the maternity ward by the psychologist and the pediatrician. The child is then examined 5 times during the first year of life (at 1, 3, 6, 9, 12 months), twice during the second year of life and then once yearly. We plan examinations of each child through childhood and adolescence. The somatic examination includes a careful evaluation of the child's health since last visit and of present health. A great number of anthropological measurements are taken. Subcutaneous fat is measured on selected sites of the body with a special caliper. Skeletal maturation is studied by means of X-ray examination of a unilateral hand, wrist and knee. Photographs in standard positions are taken. This data will give a good over all picture of longitudinal growth of Swedish children. Cross-sectional data already available on some body measurements will be expended. The main clinical feature of the study is an adequate basis for evaluation of a child's chronological growth and development. We expect the combined physical and psychological data will give useful results later, to be discussed by Dr. Klackenberg. The social background of each child is analyzed yearly. All data is collected so that transfer to a punched card system (IBM) is easily made for analysis.

G. Klackenberg and I. Klackenberg-Larsson: **The outline of the psychological part of the study.**

The maturity of mind is a biologic course that is promoted, distorted, or retarded by environmental pressure. We are going to study the personality, the emotional characteristics, social behaviour, and the intellectual abilities among children of different and various family backgrounds in a town population. To-day we know too little about the variations concerning sleeping and sleep-disturbances, childrens responses to feeding and toiletting, different forms of anxieties, jealousy, sexual behaviour,

play activity, development of locomotion and speech and so on. We will study these and other mental qualities at various age levels by interviews at corresponding time of somatic examinations. Each interview will take about 1–1½ hour. To get maximum of reliability in our interview methods we use standardized questionnaires at each age. The answers will immediately be marked in a form with many different alternatives. We have chosen as many as possible of those aspects of experience and behaviour, which are easily observed, fairly objectively described and generally thought to be of importance for the later personality. The interviews are augmented with various tests. During the first years of life a developmental test is used which is a French modification of the Gesell test. Later on the children will be tested every two years with a Terman–Merril test, alternating with a projective test. Observations will also be done on childrens play in some standardized situations. Owing to the longitudinal, intensive character of the study it is possible to correlate observations from different age levels. Results may help to clarify conflicting theories such as why do some individuals develop to mature, solid persons, while other are stiffened in childish and neurotical behavioural patterns later in adolescence. Through simultaneously done somatic observations it will be possible to study the connections between somatotype and psyche. Are the traits of character outlined by Sjöbring dominant in the very beginning of the individuals life or the result of milder infections or environmental influences? Does our knowledge of infancy make it possible to predict any of the special risks and personality characteristics that may later occur?

Discussion.—*E. Gedda.* I should like to express my satisfaction as a pediatric hygienist over investigations like those carried on by Söderling and Wallgren. Much too little attention has in Swedish pediatric research been given to developmental viewpoints, though they are of great practical importance. It may be pointed out that the attitude of the School Commission to dates for differentiation is based upon studies by a Swedish professor of psychology. Just now, however, one of the country's pedagogic journals is carrying a discussion of the question as to whether development, mental and physical, is such a discontinuous course that such important decisions may be based thereon. Not even age-characteristics so obvious to us as those distinguishing prepuberty and puberty, physical and mental, are in this connection considered to have sufficient relevance. Here medical research must come forward and present its findings.—*K. Kaijser.* In photographing children it may be difficult to get comparable body-positions in children of different ages. I should like to point out that the youngest infants may be laid on a measuring board with a foot-rest. If one raises the board to a moderate angle from the horizontal plane and takes the photograph at right angles to the plane of the angle, one may get the child in a position that is fairly comparable with the standing position. Such a photograph may undoubtedly be approved in a standardized photographic series for different ages.

G. Engleson, G. Rooth and S. Sjöstedt: **Studies on post-maturity.**

It is important to distinguish between *prolonged pregnancy*, which only refers to the duration of the pregnancy, and *postmaturity*, which refers to a particular state in the new-born infant. Postmaturity has been considered to be due to a deficient placental function, and Clifford has suggested the designation *placental dysfunction* as a synonymous term. Most earlier investigations refer more to the issue of the prolonged pregnancy. We have studied postmature infants from different viewpoints, attaching particular importance to the clinical examination. We have especially analysed the

connection between clinical symptoms of postmaturity and placental dysfunction as this may be reflected with different clinico-chemical methods. The infants have been classified in accordance with Clifford's different stages of placental dysfunction. The laboratory investigations include, inter alia, oxygen-saturation in the blood of the umbilical cord, sugar in the blood, urea, pentoses and protein-bound hexoses as well as Heller and Almén on the urine. In connection with postmaturity it has been possible to show: A gradual reduction of the oxygen-saturation with rising degrees of postmaturity, increased pentose-content in the blood of the umbilical cord, higher values for urea and non-protein nitrogen and albuminuria in over 40 per cent of the cases.

Discussion.—*B. Vahlquist.* In studies of the passage of antibodies through the placenta at the end of the 40's I had occasion to read a work by Flexner and co-workers which showed that the electrolytic exchange between mother and child is less intensive during the last month of pregnancy. The postmaturity might perhaps be regarded as an accentuation of this physiological process. The higher bilirubin level in postmature infants is probably due to the fact that also the bilirubin excretion through the placenta suffers in cases of postmaturity.

T. Skoog: **The care of harelips and cleft palates.**

Problems connected with the surgical treatment of these malformations were analysed and several solutions were illustrated with diagrams and patients who had been operated upon with different methods. Attention was drawn to the present possibility of individualized operative treatment of different degrees and types of malformation. With reference to six type-cases an account was then given of the most characteristic deformities of the skeleton and soft parts of the face that can be manifested by this clientèle at a later stage, and of the possibilities of corrective treatment existing for such cases. It is chiefly through a careful study of the secondary deformities that it has been possible to modify and improve the primary operations. The reasonable conclusion to be drawn is that the same surgeon should take charge of these cases from the first operation until the treatment is finished. Only in this way can the experience gained be utilized to the full extent to attain a better result. The interest in this part of reconstructive surgery taken by plastic surgeons is reflected in, *inter alia*, the numerous publications on the subject in the special journals and in several national and international symposia on the same. The first scientific task for the International Society of Plastic Surgeons referred, moreover, to these malformations, with a research program covering etiology, standardized criteria for diagnosis and comparison on an international basis of different methods of treatment. Swedish plastic surgeons have dealt in medical articles with different sections of this surgery and the Swedish Plastic Surgical Society has submitted to the Medical Board a proposal for the organization of the care of these malformations. This proposal is related to the division of the country that has been proposed for other specialized treatment. By giving the primary cases priority of admission at the plastic surgical departments now established in Gothenburg, Malmö, Stockholm and Uppsala it will be possible to cover the total need for treatment in our country. In these cities it will also be possible to establish the intimate collaboration between specialists (surgeon, pediatrician, dental orthopedist, phoniatrician and children's psychiatrist) that is a prime condition for completely satisfactory results with these complicated cases.

Å. Gyllenswärd and M. Michaelsson: **Measurements of portal pressure in children.**

The absence of both normal material and investigations on children with heightened portal pressure has motivated this investigation. The method adopted has been the one increasingly accepted with adults, of introducing a heart catheter so far into the portal vein as completely to occlude this. Experimental investigations on animals and experiences from man show that with this method one gets an idea of the portal pressure which is quite satisfactory for clinical purposes. Details and difficulties connected with the measurements are discussed. A material of 23 children, all normal from the viewpoint of portal pressure, and 9 measurements in 7 cases of pronounced cirrhosis of the liver are presented. Ages 4–14 years. The portal pressure is definitely lower than has been found in adults with a corresponding method. The upper normal limit is 6.4 mm Hg as against 9.7 in adults. In serious cases of cirrhosis of the liver with definite oesophageal varices a pressure of as a rule considerably more than 20 mm Hg has been found in adults, but in the present material of children only 10–15 mm.

DISCUSSION.—*E. Mannheimer.* Should not 2.5 or 3 times standard deviation have been applied instead of twice this value for the calculation of the variations of normal portal pressure? My congratulations on the results. We are in great need of the normal values given.—*E. Frisell.* At the children's department in Umeå there have in the course of 2 years been 3 cases of portal hypertension (Morbus Banti) beginning with violent vomiting of blood from oesophageal varices. The ages of the patients were 11, 8 and 2½ years. The two eldest were operated on at Kronprinsessan Lovisas Barnsjukhus with application of spleno-renal anastomosis with very good results considered after 1–1½ years. In the third case the operation was postponed for a year.

B. Jonsson and B. Strindberg: **Physical working capacity in cases of congenital heart disease.**

A study has been made of the physical working capacity in connection with different types of congenital heart disease. In a young person the physical working capacity may be normal even with a large left-right shunt. Hemodynamic studies have shown that shunts diminish during work with retention of effective heart- beat-volume. When the patient is over 30 years of age, however, the working capacity is low, which is probably due to incipient failure of the right ventricle. In cases of slight pulmonalis stenosis without shunt a normal heart-beat-volume can be maintained during work thanks to increased pressure in the right ventricle. The working capacity may therefore be normal, but at the cost of increased work for the right ventricle. With severe pulmonalis stenosis, on the other hand, the heart-beat-volume is low as is also the working capacity. With right-left shunts, too, the effective heart-beat-volume is small and the working capacity low.

C. Gyllenswärd and B. Josephson: **Changes in the concentration of some serum constituents in normal children of different ages.**

The serum concentrations of Na, K, Ca and Cl and the total protein, the protein fractions and cholesterol in normal children were determined for new-born infants and the ages 3, 6, 9, 12 and 18 months as well as 3 and 6 years. In the newly born the concentration of all the three electrolytes investigated was higher than in normal adults. K and chlorides increased steeply up to the age of 3 months but then sank slowly to

reach, at the age of 3 years, the same value as in adults. The Na-concentration sank, to reach the normal value for adults at the age of 6 months. The Ca-values were determined only for the ages 3, 6, 9 and 12 months. The value was highest at the age of 3 months, but the number of observations was too small to permit of reliable comparisons. The protein values showed marked differences as between the new-born and the age of 3 months. The albumin and γ-globulin values sank, while the α_2 and β-globulin values increased from the new-born to the age of 3 months. During childhood the α_2-value was much higher but the γ-globulin value much lower than in adults. The cholesterin concentration was low at birth and increased slowly up to the age of 6 years.

Discussion.—*N. Malmberg.* Is there any difference between the protein-values and the cholesterin-values as between breast-fed and bottle-fed children?—*B. Josephson.* It may be admitted that it is a lack in our material that we did not study the feeding of the infants. The reason for this omission was the difficulty in getting together a sufficiently large normal material at all.

L. Garby and S. Sjölin: **The value of Fe^{59} in studies on iron resorption.**

The aim of the investigation on which the lecture is based was to ascertain in greater detail the mechanism for iron resorption in children with particular regard to the question as to whether it is possible, as has been suggested by quite a number of different writers, to measure the iron resorption from the intestinal canal with the help of radioactively marked iron. It is shown theoretically that the method is unsatisfactory inasmuch as it must assume a very special case of iron-transport mechanism in the mucosa of the intestine, a special case that is a priori improbable. It is shown experimentally that, at least in infants of less than 3 months, the iron transport takes place as an exchange, and that the method is therefore, at all events for this age-group, useless.

Y. Larsson: **The islands of Langerhans in cases of pancreatic fibrosis.**

The close morphological connection between the exocrine and endocrine organic systems of the pancreas has no functional or clinical counterpart. Thus the insular function is as a rule intact even in cases of advanced pathological processes in the exocrine parenchyma. One example of this is furnished by congenital cystic fibrosis of the pancreas, mucoviscidosis, a disease in which simultaneous diabetes has been observed only in a few cases. Even the tolerance for glucose is normal in cases of intravenous injection. Patho-anatomical changes in the insular tissue have, however, been described, indicating a general structural immaturity. Opinion as to the conditions obtaining in experimental pancreatic fibrosis vary. With a quantitative method the author was able to show that where this state is produced in rabbits there is a considerable reduction in the size of the insular tissue, that at the same time an absolute alloxan-resistance occurs and that the insular tissue assumes an embryonal character. In experimentally produced hypertrophy of the pancreas, as in connection with the shutting off of the flow of bile to the intestine, the insular tissue also becomes hypertrophic. It has thus been possible, under the experimental conditions in question, to show a functional parallelism between both organic systems of the gland. Except in the case of diabetic animals the tolerance for glucose was normal both in animals

with increased insular volume and in animals in which this volume was reduced, which confirms the clinical experience that the glucose tolerance test is not sufficiently sensitive to reflect variations in the insular function otherwise than where this is reduced to diabetic level.

H. Enell and U. Hjärne: **How lasting are the effects of the Calmette vaccination of the new-born up to school age?**

The Calmette vaccination of new-born infants was begun in Stockholm at the municipal lying-in hospitals in the year 1945. In the first years this was done to a rather modest extent, and it was not until 1949 that the majority of the infants were thus vaccinated, i.e. 78.3 per cent. This voluntary method of vaccination is now so generally accepted that in the year 1955 98.8 per cent of all infants born at the Stockholm maternity hospitals were Calmette vaccinated there. During the years 1945–1955, of 150,345 infants born alive at the Stockholm lying-in hospitals, 101,391 were Calmette vaccinated. For on an average 15 per cent of these vaccinated infants the occurrence of tuberculosis in the mother or in some other member of the household was reported. These children who have been vaccinated at birth have now in increasing numbers begun to reach school age, and have in connection herewith been subjected to the tuberculin test as part of the routine health examination in the first school class. At the examinations in the years 1953–1956 the tuberculin test was carried out on, in all, 32,986 children. Of these, 15,868 had been vaccinated at the maternity hospital or during their first year of life. In the case of almost 2 per cent of these children the examination was not completed; but of the other children who had been Calmette vaccinated as infants 88.3 per cent were, after the lapse of 7–8 years, still positive to tuberculin salve, 4.3 per cent of those negative to the salve were positive to Mantoux, and only 5.5 per cent gave a completely negative reaction to tuberculin. The examination thus shows very satisfactory duration of the tuberculin allergy after Calmette vaccination in infancy, and this despite the fact that superinfections are in this material probably few. Of the non-vaccinated, a fairly constant number of pupils show spontaneous positive reaction in the examination in the first class, about 2 per cent of the total number, and this although the non-vaccinated group is successively decreasing in number. Tuberculosis is still observed, though to a rather modest extent, among teachers, charwomen and kitchen staff at the Stockholm elementary schools; thus in Jan. 1956 21 persons from these categories had sick leave owing to tuberculosis. Over and above these, a certain number of cases under control are allowed to serve in the schools, in consideration of the diminished risks in the elementary schools thanks to the Calmette vaccination.

Discussion.—*A. Wallgren.* The persistence of BCG-immunity has been the subject of lively discussion and is of course of great importance with regard to the practical application of BCG-vaccination. The Swedish vaccine has always had a high percentage of cases in which the vaccine has taken, without provoking all too strong local reactions, and Ennell's investigation shows, moreover, that the tuberculin sensitivity remains for at least 7 years. Andersson and Belfrage had a similar experience in Gothenburg in 1939. Since according to Ennell the sources of infection in Stockholm appear to be very few, it is unlikely that virulent infection should to any great extent be responsible for the remanent tuberculin sensitivity. It is for this same reason, the slight risk of exposure, that I have been dubious of the retention of mass-vaccination

of the new-born, and the strong natural resistance of children of earlier school-age has seemed to me sufficient to protect them from serious forms of early tuberculosis. I have therefore considered prepuberty to be the most suitable age for vaccination; the children and young people will then get increased resistance at a sensitive age in which the risks of infection are undoubtedly greater.

S. Krœpelien: **Viewpoints concerning the prognosis for asthma in children in the light of respiration studies.**

The total capacity (V_{TLC}) and its subdivisions, as well as the "first-one second capacity" in 98 and 43 entirely *symptom-free* asthmatic children aged 6–14 years. The results obtained have been compared with the corresponding values in healthy children. The degree of severity of the children's asthma has been clinically classified in 3 groups according to the frequency of the attacks. The asthmatic children show the same vital capacity (V_{VC}) as healthy children, while their functional residual capacity (V_{FRC}) and residual volume (V_R) are considerably increased. The V_{FRC}/V_{TLC} and V_R/V_{TLC} quotients are also increased. The median respiratory position is displaced to the inspiratory side, which paves the way for the appearance of the actual emphysema. The changes are most pronounced in the group of children having the most frequent asthma trouble. The "first-one second-capacity" (the percentage of V_{VC} which from the maximal inspiration position can be exhaled during the first second) also shows results completely divergent from normal conditions, and here, too, the divergence is most pronounced for the group having the most frequent attacks. Through comparisons before and after the administration of Isoprenalin in aerosol and Theophylline intravenously a certain normalization of the static lung-volumes has been shown in different groups of asthmatic children; but the difference is still great in relation to healthy children. The results support the assumption that the changes shown are only to a certain extent bronchospastically conditioned. Many asthmatic children show clear signs of pulmonary insufficiency, which is probably only to a certain extent functionally conditioned. As a rule it is only asthmatic children in whom the condition is very pronounced who show direct manifest symptoms of insufficiency, and in the majority of cases the insufficiency is latent and is not revealed until functional tests are applied. There are strong reasons for the assumption that pulmonary insufficiency manifested at an early stage is unfavourable for subsequent development and worsens the prognosis for asthma considering the risk of symptoms of cardio-respiratory insufficiency appearing later. The frequent occurrence of pulmonary insufficiency is a strong argument in favour of asthmatic children getting a rational and adequate therapy as early as possible.

Discussion.—*Å. Gyllenswärd.* My congratulations especially on the solution of the difficult problems of method connected with respiratory examinations carried out on children. And now a couple of questions: How has the author assured himself that the patients have been quite free of asthma on the occasion of the examination? As is known from other investigations, there is a subclinical asthma. May not the rather gloomy results in the worst group have been due at least in part to the fact that the patients were not in a really free interval? Has the author investigated the maximal respiratory capacity of the asthma patients, and what results has he arrived at in this connection?

J. Bergstedt and R. Lundström: **Can gamma-globulin prevent nosocomial infections at an infant department?**

A controlled study has been carried out at Kronprinsessan Lovisas Barnsjukhus for a period of one year with gamma-globulin in order to ascertain its capacity to prevent nosocomial infections. In a series of 210 infants, gamma-globulin was given to every other child on arrival at the department, while a placebo preparation was given to the others. The result supports the assumption that with the dosage applied and in the authors' material gamma-globulin had a prophylactic effect as regards infection.

B. Hallgren, K. Linneroth, K. Palmén and R. Zetterström: **Primary rickets refractory to D-vitamin, an hereditary metabolic disease.**

An investigation on the relatively rare metabolic disease, primary rickets refractory to D-vitamin, covers 16 primary cases belonging to 12 families. In these families both the affected and the non-affected members have been examined, firstly with a routine clinical examination, and secondly with serochemical analyses of calcium, phosphorus and alkaline phosphatase. In three of the families one of the parents was found to be clinically affected. In a younger brother of one of the cases it was possible to diagnose the disease on the basis of serochemical and roentgenological changes before the appearance of any skeletal deformities proper. Examination revealed a number of cases that have been designated as "subclinical". These have distinct but not definitely pathological curvings of the extremities or only serochemical changes such as reduced phosphate concentration or increased alkaline phosphatase activity. In those families in which the one of the parents of the primary cases is clinically affected, more than half of the sibs are affected. The disease has in the majority of cases proved to be hereditarily conditioned. It is in 4 families clearly dominant, in one family-line it can be followed for 4 generations. In a further 2 families the heredity is probably dominant. In the other families it has not been possible to determine the heredity with certainty. At the present stage it is therefore not possible to decide whether the disease is genetically uniform. In two families the fathers or mothers are sibs; it has otherwise not been possible to connect the families, despite the fact that in certain cases the genealogy has been followed back to the 18th century.

F. Heijkensköld and J. Winberg: **Moncrieff's syndrome—hiatus hernia, mental deficiency and sucrosuria.**

Account of a case of Moncrieff's syndrome—a 10-year-old boy with hiatus hernia, pronounced mental deficiency and sucrosuria. Of 5 cases of hiatus hernia at the clinic 2 are definitely mentally defective, without any definitely known genesis, while a third case is suspected of mental deficiency. Only one of two examined cases excreted sucrose. The disease is presumed to have a recessive heredity. A genetic investigation is under way.

S. Edlund: **Manifestations of the Schönlein-Henoch syndrome.**

Discussion.—*V. Oldfelt.* During the past 10 years at the Children's Department of the Linköping Hospital we have had 42 cases of Henoch-Schönlein's purpura, including 20 cases during the last 2 years, which we think a remarkable crowding. Of these cases, moreover, ¾ have occurred in the late summer and early autumn,

which is a time of year in which no increase of streptococcal infections has occurred, and which we have thus in general not been able to connect with purpura, even if in certain cases there has been an increased anti-streptolysine titer. We have instead suspected some alimentary cause. In some cases there has been an intestinal infection at the same time as hemolytic streptococci have appeared in the pharynx. As some cases, also at our hospital, have been extremely serious, it seems desirable to trace the cause, which still seems rather obscure.—*K. Kaijser.* An investigation of the cases of definite Schönlein-Henoch syndrome in the form of purpura that we have had at the children's department in Eskilstuna has revealed the following special features.—1. Seventy-three per cent of all the cases occurred during the last 6 months of the year, with the maximum in October and November.—2. The cases admitted to our hospital have increased in number with each year.

P. O. Hillborg: **Eleven cases of Morbus Gaucher from Norrbotten county.**

Although Morbus Gaucher is a rare disease, in all 11 cases of it have in the past 20 years been treated at the Garrison Hospital in Boden and at Gällivare Hospital. Of these 11 cases, 7 have occurred during the past 4 years. In other reports of the disease a large number of the patients are adults, but in this material there is no case over the age of 16 years, and in the whole of Norrbotten County there is no adult registered with the disease. Five of the 11 have died. The material includes 3 groups of sibs and one pair of cousins. Seven families are represented. In all of the cases except one the diseases was first manifested at the age of 1 year in the form of enlarged spleen, anaemia or tendency to bleeding. In one case the first manifestation was at the age of 5 months, and this patient had several neurological symptoms, which were absent in the others. In 8 cases splenectomy was performed. In all the cases the spleen was much enlarged. The largest of the removed spleens weighed 3.1 kg. Before the operation hemorrhagic tendency was observed in 5 cases and tendency to infection in 7 cases. All the patients were suffering from anaemia, which improved after the operation in those whose spleen was removed. The number of white blood corpuscels before the operation was either low or normal, in all cases it was markedly increased after the splenectomy. Before the operation the number of thrombocytes was subnormal in all the patients, but rose after the operation to normal values. With the help of sternal or tibial punctates it was in 9 of the cases possible to make the diagnosis before the operation. After this it was definitively established through PAD on the spleen. When the disease has persisted for a longer period, skeletal changes often occur. The 3 oldest patients, aged 9, 11 and 16 years, have pronounced symptoms of this kind in the form of vertebral kyphosis, thickening of the metaphyses of the long bones or hip changes. As a rule the patients have been treated before the operation, sometimes for several years, with peroral iron therapy and blood transfusions, This has resulted in temporary improvements in the blood-values and in the general condition of the patient. The extirpation of the spleen has had a good and prolonged effect upon the hemoglobin-value, the number of white blood corpuscles and platelets.

Meeting Jan. 11, 1957 together with the Section for Acute Infectious Diseases

J. Ström: **Allergic reactions in the treatment of hemolytic streptococcal infections with probenecide-containing penicillin preparations.**

(To be published in *Acta Pædiatrica 46:* 1957.)

S. Gullberg: **Two cases of transverse myelitis.**

Two cases are shown from 1956 at the Stockholm Epidemic Hospital. 1) A 13-year-old boy who in connection with an aseptic meningo-encephalitis developed pareses of the legs, loss of sensibility, bladder paresis lasting for 3 weeks. In 3 months he was completely recovered, except for deficient sphincter-control and slight mental disturbances. 2) A 10-year-old girl who in connection with varicellae developed an opticus-neuromyelitis with almost blindness and total paralysis of the legs. Loss of sensibility as far up as the ensiform process. Bladder paresis for five months, thereafter automatic evacuation. After 1 year walking with crutch-sticks; still considerably spastic. Sight up to standard. Sensibility normal.

Discussion.—*B. Vahlquist.* In a number of cases of transverse lesions it is not possible to show any releasing cause. One may here ask oneself whether the injury may not be an expression for a first attack of disseminated sclerosis. I should like to ask Gullberg whether in the Boston material there is any mention of relapses of the disease. I should also like to put a question concerning the therapy. In a case I saw 3 years ago, a 13-year-old girl, laminectomy was performed, as the possibility of a tumour could not be definitely excluded. The exposed spinal cord showed such an intensive edema that the neurosurgeon had to leave a fenestra to relieve the pressure. Perhaps a more active, surgical therapy may be indicated in some of the cases in question.—*S. Gullberg.* The prognosis is considerably better in the case of younger individuals. The writers referred to state that the prognosis is debatable in view of possible residues and the tendency to recidivation.—*G. Öberg.* The time for the appearance of these complications and the patho-anatomical picture show remarkable points of agreement in cases of varicellae, morbilli and postvaccinal encephalitis. In certain cases there is doubtless a considerable edema. A little over a year ago I observed a varicellae-encephalitis with hemiplegia, serious EEG changes and a papillar protrusion of 2 diopters, where all these symptoms disappeared in a couple of days in connection with thereapy against the inflammatory or allergic edema.—*S. Gullberg.* Only 1 week after the onset of the varicella she had impaired sight, and 14 days after onset the ophthalmologist stated papillar edema and protrusion of 2–3 diopters.—*B. Holmgren.* A couple of cases are described in which laminectomy has been performed in the acute stage and a fenestra made to relieve the local edema with quicker healing. Suitable to combine with local and general cortisone treatment on analogy with what has been done in cases of severe encephalites and myelites in cases of mononucleosis. A case described with high fever and dazed condition in which large doses of cortisone were given with quick restitution within 36 hours.—*G. Öberg.* I used corticosteroids in the case of the previously mentioned varicellae-encephalitis and also with two morbilli-encephalites, the one combined with polyradiculitis. In all cases with very quick regression. I consider that a brief but sufficiently strong dosage of corticosteroids is motivated in the acute stage of these neurological complications.

L. Adolphson: **Case of septic spondylitis.**

A 12-year-old school-girl, who had previously always been healthy. Became acutely ill at midsummer with pains in the right groin radiating into the small of the back. Appendix removed on suspicion of appendicitis; appendix normal, however. Another physician diagnosed her trouble as caused by an infection of the urinary passages, and she was treated with terramycin. Pains in small of back persisted the whole time, with occasional periods of fever with temp. about 38°C. Examination at beginning of August revealed gibbus in lower thoracal region and atrophy of dorsal musculature suspected. Her condition was interpreted as status post polio and she was remitted to the Epidemic Hospital. On admission on the 6/8 distinct kyphotic position of the lower thoracic part of the back was observed, with restricted mobility in all directions. Status otherwise physically normal. Afebrile. S.R. 20 mm. AST 400. Asta 22. Roentgen examination of spine on admission showed suspect changes in Th XII. In the light of the onset, the repeated periods of fever before admission, the raised S.R. and the raised Asta-values the case was interpreted as a septic spondylitis (staphylococcal infect.), in spite of the uncertain roentgen findings. Treated with erythromycin for 4 weeks, which resulted in a distinct clinical improvement. A subsequent roentgen control revealed distinct destructions in Th XII and the picture was now considered to agree with the diagnosis of spondylitis. In the sequel entirely free of subjective symptoms. Afebrile, normal S.R. Asta-values still heightened. Discharged after 1 month free of symptoms. Planigraphy just before discharge: stat. quo.

B. Lamberger: **Peculiar form of meningococcal meningitis in connection with inoculation against smallpox.**

Report of a case of meningococcal meningitis in connection with vaccination against smallpox in a 10 months old boy. The rôle of smallpox vaccination is discussed, and the possibility that it is a matter of an uncommon and less pathogenic type of meningococci, since the course of the disease has been benign and pathogenetic examinations carried out on animals may possibly indicate this. Another peculiar circumstance is that after 2 weeks' sulfa and penicillin treatment bacteria were still found in the liquor.

Discussion.—*H. Ericsson.* As a bacteriologist I should like to ask for an explanation of a couple of remarkable circumstances in the case reviewed. 1) Why was it so long before the bacteriological diagnosis was made? 2) Why were such relatively small doses of penicillin employed? Alexander suggests much bigger doses, and we have had good experience with the application of her principles. 3) Was there any attempt to ascertain whether the therapy had resulted in adequate concentrations in the central nervous system? As we know, there are methods for a simple and quick control of concentrations in small amounts of fluid (Ericsson et Wickman, Acta pathol. & microbiol. Scand. Suppl. 111, 1955). 4) It seems extremely improbable that the meningococci should have become restistant to penicillin as the lecturer assumed. Resistant strains of meningococci, gonococci, β-hemolyzing streptococci, pneumococci and syphilis spirochetes have hitherto never been shown.—*G. Tunevall.* The bacterial findings in the three positive cultures extremely sparse, perhaps indicating a circumscript process, difficult to get at with therapeutics. The results of the determinations of resistance are now available and show no increased resistance.—*B. Vahlquist.* The lecturer mentioned that the coincidence of vaccination and meningococcal infection might be explained either by a previously existing infection of this kind or vice versa.

In this connection it may be worth reminding you of the concept of sub-sepsis, which in certain cases manifests itself as Wissler's disease and among whose causes chronic meningococcemia has been mentioned.

J. Pejme: **Three years' observation of the paretic polio cases from the Stockholm epidemic 1953.**

The work has been performed in collaboration with social worker I. Bergholtz and qualified physiotherapist M.-B. Lennmarken. (Published in Acta med. Scandinavica.) In the 1953 epidemic there were 633 patients with pareses. Of these, 388 or 61 per cent were quite healthy after three years' observation. Ninety-six or 15 per cent can go to work despite invalidity. Qualified care (continued hospitalization or the equivalent) is given to 26 patients. Thirty-two or 5 per cent have died. The number receiving a clean bill of health is high, although the epidemic was severe, as is shown by the displacement to higher age-groups and by the large number of cases of respiratory insufficiency with a marked frequency of respirator treatment among these.

Meeting February 2, 1957

Jernelius, B.: **Cerebral injury after over-heating and triple vaccination.**

In July a 3-months-old infant was admitted to hospital; the child had been left for 2 hours in a car which was parked in the sun and was in a very bad condition. He was pale, in a cold sweat, dehydrated, had a stiff neck and a rectal temp. of 40.5°C. He recovered quickly with the help of stimulants, cooling off and fluid injected subcutaneously. The following day he had a temperature peak of 39°C but was subsequently free of fever. He was in the sequel free of symptoms and continued to develop normally. At the age of 4 months the child was triple-vaccinated for the first time. In connection with the second triple vaccination at the age of 5 months the boy became feverish and vomited for a week. After this period he became apathetic, stopped grasping, babbling and smiling. His condition has since deteriorated successively and he now appears completely decerebrated and shows signs of hydrocephalus.

With reference to the literature different etiologies of the child's cerebral insult are discussed. 1) *Over-heating* alone not a probable cause in view of the long period of latency. 2) *Vaccination encephalopathy*, in connection with which the over-heating may possibly have facilitated the occurrence of the cerebral insult, seems most likely in this case. 3) *Encephalitis* which by a coincidence gave rise to symptoms at the same time as the child was triple-vaccinated is conceivable but not very probable.

On account of this case and because in the literature it is considered that vaccination encephalites afflict in particular children with cerebral insults, the author has performed experiments on animals. Rabbits of different ages were exposed to an extreme temperature of 50–60°C for 1 to 2 hours and then triple-vaccinated after different latency periods. Those that survived the acute over-heating, however, suffered no ill-effects from the vaccination.

Discussion.—*Nordwall U.* The lecturer mentioned that care should be taken with triple vaccination where there is heredity for allergy. In spite of years of triple vaccination, of course also including a large number of children with allergic relatives, no complications have been observed. Have others had any other experiences?—*Sjölin, S.* Em-

phasized that a triple vaccination may be regarded as the cause of a cerebral insult only where there is a close connection in time between the vaccination and the cerebral symptoms. In 1955 Low gave an account of 38 cases of vaccination encephalopathy. Of these, 30 had shown symptoms within 18 hours, 34 within 24 hours. The literature gives no support for the assumption that allergic children or children with allergic heredity run greater risks of vaccination encephalopathy than healthy children.—*Nordenfelt, P.* I do not consider it desirable for the triple vaccinations to be performed at the Children's Welfare Centre.—*d'Avignon, M.* I have been performing triple vaccinations at the Children's Welfare Centre since 1952. This entails no inconveniences at all as regards the children, provided it is performed in infancy, at the age of 3, 4 and 5 months. The reactions of the infants are very slight, and no fearful memories that might occasion difficulties on later visits to the Children's Welfare Centre have been observed.—*Gyllenswärd, C.* Is not serum against tetanus given in accident cases despite the fact that the patient has been triple-vaccinated?—*Ekström, G.* Not at Kronprinsessan Lovisas Barnsjukhus.

Hedqvist, T.: **Follow-up study of stunted children.**

An account is given of a material of 23 stunted patients (13 girls, 10 boys) who had attained adult age. At the first examination they had not manifested any definite signs of endocrine or other affections. In many cases the prognosis for growth proved to be poor. Among the men the height was in 5 cases clearly below the lower dispersion limit according to Broman-Lichtenstein-Dahlberg's normal values; the corresponding number among the girls was 7. The poorest prognosis for growth referred to the group of boys with evidently retarded skeletal development, of whom the majority as adults gave the appearance of sexually infantile dwarfs. In five of the girls it was possible to diagnose a certain or probable gonad-dysgenesia (or so-called agenesia ovarii), but none of them manifested a clear Turner's syndrome. The importance of always reckoning with the possibility of gonad-dysgenesia in stunted girls is emphasized. The possibility of judging the prognosis for growth in the individual case after a single examination before the age of puberty seems to be slight or non-existent.

Bergstrand, C. G. and Czar, B.: **Paper-electrophoretic examination of fetal serum.**

Serum from 34 fetuses and mothers was examined with paper-electrophoresis according to Dettker & Andurén. The fetuses derived from a series of legal abortions where the pregnancy had been terminated owing to weakness in the mother. The length of the fetuses varied between 10 and 27 cm. The amount of total protein in the serum and the relative and absolute amounts of the different protein fractions in the mother and the fetus are shown in diagrams. The occurrence of a new serum-protein fraction not previously mentioned in the literature is demonstrated. This fraction, which in the strip of paper is situated between the α-globulin and the albumin, was found in all the fetuses but not in the mothers. Nor could it be shown in prematures (lowest weight at birth 1550 g). After zone-electrophoretic fractioning the unknown protein was again shown at α-globulin and albumin with the help of paper-electrophoresis. The unknown protein seems to be reduced with increasing age in the fetus. The investigation will be published later.

Thorén, C.: **Tetanus in children. A clinical survey.**

An 11-year-old girl was admitted last summer to the medical clinic of Kronprinsessan Lovisas Barnsjukhus with tetanus. The onset came 2 weeks before admittance in the form of tenderness in one cheek and difficulty in opening the mouth. No known focus of infection. Short-wave treatment gave no alleviation. Finally, only liquid food could be taken. Besides trismus, there was a general increase of tonus, most pronounced in the musculature of the neck and the abdomen. A classical picture of tetanus rapidly developed, though without merging into convulsive seizures. Narcosis did not prove necessary but was held in readiness for emergency developments. Human antitetanus serum from the Blood Donors' Centre at Karolinska sjukhuset was given intravenously without reactions. There was successive slow improvement hereafter.

Fifteen cases of tetanus in children in Stockholm during the last 10 years have been collected for comparison, the majority aged 6–8 years. Ten had a localizable source of infection, but owing to the slightness of the wound only 4 were given primary surgical treatment. There was no specific tetanus prophylaxis in any of the cases. Five had no demonstrable infection. Seven had symptoms for more than 1 week before the diagnosis was made. Where this was known, the incubation period showed clearly that a short period implies a poorer prognosis. All 4 with an incubation period of less than 1 week died. The number of deaths was 6. The mortality was thus higher than in adults. The causes of death were pneumonia, heart failure and asphyxia. Diagnostic difficulties were common. Abdominal symptoms were in some cases misleading. In some cases hysteria was suspected. Difficulties in chewing are often an early symptom. One third of the cases were without demonstrable infection. Trifling injuries such as abrasions and pricks do not as a rule entail surgical treatment, but may explain some of the numerous so-called cryptogenic cases.

Interest in general inoculation against tetanus is at present very great all over the world. The goal is firstly to reduce the number of cases of tetanus and secondly to replace the serum prophylaxis with something innocuous and more effective. To enlist the fear of whooping cough to obtain he assent of parents to triple vaccination is medically defensible. The vaccination should be done through the Children's Welfare Centres, which is unfortunately not always the case. About thirty cases of tetanus a year do not perhaps, *in et per se*, motivate a public campaign for vaccination as extensive as that now being carried on for vaccination against polio, but more propaganda is needed.

B. Gullbring: **Treatment of tetanus with human serum.**

It has been common practice in the treatment of tetanus to include in the therapeutic arsenal also passive immunization with antitoxic serum from horse. The administration of protein from another species—in this case horse serum—often leads to the formation of antibodies in the recipient. In view of the possible serious consequences of this, e.g. in the form of serous disease or, on renewed administration, anaphylactic shock, I have produced human antitoxic serum from blood donors who have been actively immunized with toxoid. From these persons one obtains, even after only 3–4 inoculations of toxoid given at suitable times, serum concentrations of antitoxin of 10–20 AU/ml. It has also been possible to obtain serum concentrations of 150 AU/ml (I. Shiebel, Copenhagen, personal communication). The advantages of human antitoxin follow from the elimination of the risk of sensibilization to protein from other species. Thus repeated administration of varying volumes is possible.

The antitoxin may be administered intravenously. The disadvantages would in the main follow from the relatively lower content of antitoxin per unit volume in human serum. Apart from the compensation implied in larger volumes and repeated administration, mention may also be made of the possibility of using gammaglobulin from such serum. Such gammaglobulin I have been able to produce through the kindness of AB Kabi; it gives e.g. 300 AU/g from serum with a content of 6 AU/ml. A serum concentration of 0.1 AU/ml in the patient is generally regarded as a protection, and even the value 0.05 AU/ml has been mentioned. In order to obtain such a value for the longest possible time in connection with the administration of antitoxic serum from horse, it has been attempted to give relatively large amounts of antitoxin initially. In the case described by Thorén about 3,600 AU of human antitoxin was administered in two infusions. Analyses carried out every 5th day during the first 30 days after the first infusion showed an antitoxin concentration above the value 0.1 AU/ml, and on the 58th day the concentration was still 0.065 AU/ml. During this period the patient was not in any other way passively immunized or artificially actively immunized. Preliminary titrations were carried out at the State Bacteriological Laboratory, and thereafter at the State Serum Institute, Copenhagen.

L. Thorén: **Tetanus in infants.**

A. *Prophylaxis.*

1. Active immunization. The infants should be triple-vaccinated and also be given a "booster dose" when they begin school. 2. Passive immunization in connection with the injury does not give full protection. Anaphylaxis and serum disease make a restrictive attitude to serum prophylaxis defensible. 3. Surgical treatment of the wounds to eliminate anaerobic milieus and infection prophylaxis.

B. *Treatment.* Experiences from the surgical clinic in Uppsala.

1. Specific treatment with serum with high dosage. We have given about 100,000 IU per 24 hours for 4–5 days. In those cases in which the primary foci were not found the serum treatment has been prolonged. 2. Anesthesia. Of great importance is a more careful supervision by staff trained in the administration of anesthetics. This supervision must be kept up for about a week after the last seizure, as an unexpected isolated seizure may otherwise have fatal consequences. Tracheotomy is recommended in all cases in which the diagnosis of tetanus is made. 3. Surgical cleaning up of a wound should always be performed under narcosis. 4. Symptomatic pharmacological treatment is given according to the degree of seriousness and stage of development of the disease. (*a*) Sedatives and analgesics (avertin, barbiturates, paraldehyde, pethidine etc.) may sometimes be sufficient. (*b*) Myanesin together with sedatives and analgesics is given in somewhat more severe cases. Myanesin is administered in 1–2 per cent solution with control of possible hemolysis in the blood during the treatment. (*c*) Neuromuscular blockade (curare, succinycholine) with respirator treatment is given in the most serious cases. 5. Infection prophylaxis with antibiotics and physical atelectasis-pneumonia prophylaxis. 6. Nutrition. On account of the high metabolism with tendency to acidosis, high caloric solutions are administered with a duodenal catheter or parenterally. In certain cases a jejunostomy is indicated. 7. Treatment of hyperthermia. The hyperthermic states not due to pneumonia are often bad signs

in tetanus cases. They are probably released from the diencephalon. They can be eliminated or improved with hibernal-lergigan-pethidine and physical surface cooling, and this treatment may possibly save the patient's life in some cases. Prolonged hypothermy has also been suggested for tetanus cases, but we have no experience of this. 8. During the relatively long period that the patient's own defence mechanisms are not functioning sick care of the very highest class is necessary.

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